

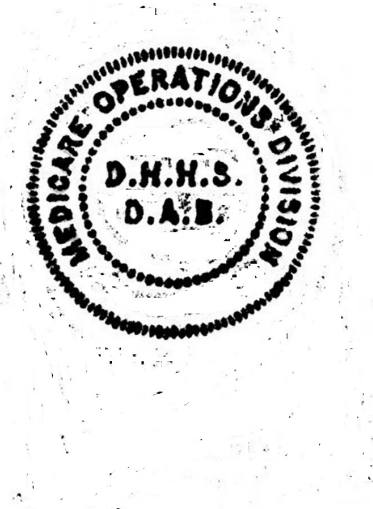
United States of America


Department of Health and Human Services

CERTIFICATION OF TRUE COPY

Pursuant to the provisions of 42 U.S.C. 3505 and the authority vested in me by delegation from the Secretary (See attached), I hereby certify that the annexed are true copies of the documents on file in the Department of Health and Human Services.

IN WITNESS WHEREOF, I have set my hand and caused the seal of the Department of Health and Human Services to be affixed, on this 21st day of April, 2020.





Angela Roach
Executive Director and
Administrative Appeals Judge

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF WISCONSIN

| | | |
|------------------------------------|---|----------------------|
| DAVID CHRISTENSON |) | |
| |) | |
| and |) | |
| |) | |
| ANNIKEN PROSSER, |) | |
| |) | |
| |) | |
| |) | |
| Plaintiffs |) | |
| |) | |
| v. |) | |
| |) | Civil Action Number: |
| SECRETARY of the |) | |
| UNITED STATES DEPARTMENT OF HEALTH |) | 1:20-cv-00194-WCG |
| AND HUMAN SERVICES, |) | |
| |) | |
| |) | |
| Defendant. |) | |
| |) | |
| |) | |

ADMINISTRATIVE RECORD

David Christenson & Anniken Prosser
Appellant

David Christenson & Anniken Prosser
Beneficiary

1-8630709341 & 1-8390277469
ALJ Appeal Numbers

David Christenson & Anniken Prosser,
Plaintiffs

v.

Secretary of the United States Department of Health and Human Services,
Defendant.

Court Identification Number: 1:20-cv-00194-WCG

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¹ The Council notes that the ALJ's pagination omits pages 247 through 785. However, the Council confirmed with the contractor (AdQIC) that the Council received the entire claim file. Additionally, ALJ Exh. 1 includes a CD that was submitted by the appellant. A copy of that CD is included with this record and can be found in a subfolder named "CD Attachment #1."

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² ALJ Exh. 4 includes a CD that was submitted by the appellant. A copy of that CD is included with this record and can be found in a subfolder named "CD Attachment #2."

³ ALJ Exh. 3 includes a CD that was submitted by the appellant. A copy of that CD is included with this record and can be found in a subfolder named "CD Attachment #3."



Departmental Appeals Board, MS 6127
Medicare Appeals Council
330 Independence Avenue
Cohen Building, Room G-644
Washington, DC 20201
(202)565-0100/Toll Free:1-866-365-8204

Date: **JAN 22 2020**

ALJ Appeal Numbers: 1-7884275431 & 16 others
Docket Numbers: M-19-1261 & 30 others

ACKNOWLEDGMENT OF ESCALATION REQUESTS
AND NOTICE OF STAY

Parrish Law Offices
Debra Parrish
788 Washington Rd.
Pittsburgh, PA 15228

Dear Ms. Parrish:

The Medicare Appeals Council (Council) has received your requests to escalate the appeals listed in Attachment A to Federal district court. The Council previously received your requests for review for these appeals. The 90-day time frame for the Council to issue a decision, dismissal, or remand order has expired. *See* 42 C.F.R. § 405.1100(c). Due to the large number of pending appeals, the Council is unable to issue a decision, dismissal, or remand order within five calendar days of your request to escalate to Federal district court. 42 C.F.R. § 405.1132(a)(1). Under these circumstances, the regulations permit you to bypass Council review and seek review of the ALJ's decisions in Federal district court. 42 C.F.R. § 405.1132(a)(2).

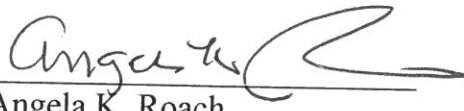
In order to escalate, you must file an action in Federal district court within 60 calendar days after you receive this notice and the amount in controversy must be \$1,670 or more. 42 C.F.R. §§ 405.1132(b), 405.1136(a)(1); *see also* 84 Fed. Reg. 53,445 (Oct. 7, 2019). If you cannot file your complaint within 60 days, you may ask the Council to extend the time in which you may begin a civil action. However, the Council will only extend the time if you provide a good reason for not meeting the deadline. Your reason must be set forth clearly in your request. 42 C.F.R. § 405.1134. If you do not file an action in Federal district court, then your appeals will remain before the Council. 42 C.F.R. § 405.1136(a)(2).

If a civil action is commenced, the complaint should name the Secretary of Health and Human Services as the defendant and should include the Council docket numbers and ALJ appeal numbers that you are appealing. 42 C.F.R.

§ 405.1136(d). The Secretary must be served by sending a copy of the summons and complaint by registered or certified mail to the General Counsel, Department of Health and Human Services, 200 Independence Avenue, S.W., Washington, D.C. 20201. In addition, you must serve the United States Attorney for the district in which you file your complaint and the Attorney General of the United States. *See* rules 4(c) and (i) of the Federal Rules of Civil Procedure and 45 C.F.R. § 4.1.

Additionally, the supplier filed a separate request for review in each of the appeals for which you seek escalation. *See* Attachment B. This letter serves as notice to all parties that the Council will stay the supplier's requests for review until the Federal district court issues a final determination on the escalated appeals or the time period for filing a complaint in district court expires.

Sincerely,


Angela K. Roach
Administrative Appeals Judge

cc: Novocure
Beneficiaries

Attachment A

Appeals Escalated to Federal district court

| Docket Number | ALJ Appeal Number(s) |
|---------------|-----------------------------|
| M-19-1261 | 1-7884275431 |
| M-19-2164 | 1-8411344383 |
| M-19-2173 | 1-8136495060 |
| M-19-2218 | 1-8411055191 & 1-8411055450 |
| M-19-2233 | 1-8390277469 |
| M-19-2426 | 3-8503660334 |
| M-19-2499 | 1-8429561876 |
| M-19-2560 | 1-8454636221 |
| M-19-2648 | 1-8510955262 |
| M-19-2649 | 3-8472551932 |
| M-19-2719 | 1-8393258352 |
| M-19-2723 | 1-8411066311 |
| M-19-2777 | 1-8630709341 |
| M-19-2780 | 1-8415607840 |
| M-19-2836 | 1-8665714599 |

Attachment B

Stayed Supplier Appeals

| Docket Number | ALJ Appeal Number |
|------------------------|-----------------------------|
| M-19-1380 | 1-7884275431 |
| M-19-2169 | 1-8411344383 |
| M-19-2179 | 1-8136495060 |
| M-19-2227 | 1-8411055191 & 1-8411055450 |
| M-19-2237 | 1-8390277469 |
| M-19-2275 ¹ | 1-8071086400 |
| M-19-2543 | 3-8503660334 |
| M-19-2542 | 1-8429561876 |
| M-19-2565 | 1-8454636221 |
| M-19-2750 | 1-8510955262 |
| M-19-2751 | 3-8472551932 |
| M-19-2810 | 1-8393258352 |
| M-20-75 | 1-8411066311 |
| M-19-2981 | 1-8630709341 |
| M-19-2985 | 1-8415607840 |
| M-19-2990 | 1-8665714599 |

¹ The beneficiary appeal associated with docket number M-19-2275 is docketed as M-19-2250. The Council previously acknowledged the beneficiary's request to escalate her appeal in a separate action.

PARRISH LAW OFFICES

788 WASHINGTON ROAD
PITTSBURGH, PENNSYLVANIA 15228-2021
www.dparrishlaw.com

412.561.6250
FAX 412.561.6253
E-mail: info@dparrishlaw.com

January 3, 2020

VIA E-file

Department of Health and Human Services
Departmental Appeals Board
Medicare Appeals Council, MS 6127
Cohen Building Room G-644
330 Independence Ave., S.W.
Washington, DC 20201

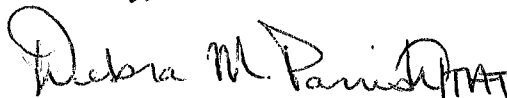
RE: Request for Escalation
Appellant/Medicare Beneficiary: David Christenson
HICN: 7QR9QM0QP33
ALJ Decision Date: Sept. 12, 2019
ALJ Appeal No.: 1-8630709341
Council No.: M-19-2777 (filed Sept. 18, 2019)
Our Ref: 19-296

Dear Medicare Appeals Council:

Mr. David Christenson has received three favorable ALJ decisions finding TTFT meets Medicare coverage criteria for him. See ALJ Nos. 1-8285652321, 1-8416229632 and 1-8416270832. The Secretary chose not to appeal the decisions and each of them has become final. The Secretary is barred by the doctrine of collateral estoppel/issue preclusion from re-litigating those issues with respect to Mr. Christenson. As noted by a unanimous Supreme Court, "We have long favored application of the common-law doctrines of collateral estoppel (as to issues) and res judicata (as to claims) to those determinations of administrative bodies that have attained finality." See *Astoria Federal Savings and Loan Assoc. v. Solimino*, 501 U.S. 104, 107-8 (1991) (internal citations and quotations omitted). The application of issue preclusion would not work as basic unfairness against the Secretary and there are no special circumstances that would make it unfair to apply the doctrine.

The above-captioned Medicare beneficiary appeal has been pending for more than 90 days. Accordingly, pursuant to 42 C.F.R. §405.1132, Mr. Christenson requests escalation of the above-captioned claims to District Court.

Sincerely,



Debra M. Parrish for
Medicare Beneficiary David Christenson

Enclosures: Three Final Favorable ALJ Decisions

cc: David Christenson
Novocure
C2C



Department of Health and Human Services
Office of the Secretary

OFFICE OF MEDICARE HEARINGS AND APPEALS

Cleveland Field Office
200 Public Square, Suite 1300
Cleveland, OH 44114-2316
216-615-4000 (Main)
216-615-7549 (ALJ Tyler Team)
216-615-7124 (Fax)
866-236-5089 (Toll Free)

Date: April 2, 2019

Debra M. Parrish
788 Washington Road
Pittsburgh, PA 15228

NOTICE OF DECISION

Appellant: D. Christenson
OMHA Appeal Number: 1-8285652321

Enclosed is the decision for the above case. This decision is based on the administrative record, including any evidence or testimony presented at the hearing, if one was held. The decision is not precedential, does not release the appellant from civil or criminal liability, and may be reopened at any time if it was procured by fraud or similar fault. In addition, the decision may be reopened within 180 calendar days from the date of the decision for good cause. Good cause exists when there is new and material evidence that was not available or known at the time of the decision and may result in a different conclusion, or when the evidence that was considered clearly shows on its face that an obvious error was made at the time of the decision.

What if I disagree with the decision?

If you disagree with the decision, you may file an appeal with the Medicare Appeals Council. Other parties may also appeal the decision. In addition, the Medicare Appeals Council may decide to review the decision on its own motion. If no party appeals the decision and the Medicare Appeals Council does not review the decision, the decision is binding on all parties and you and the other parties will not have the right to ask a federal court to review the decision.

If you are not already represented, you may appoint an attorney or other person to represent you.

How much time do I have to file an appeal?

The Medicare Appeals Council must receive your written appeal **within 60 calendar days** of the date that you receive this notice. The Medicare Appeals Council assumes you received this notice 5 calendar days after the date of the notice unless you show that you did not receive it within the 5-day period.

The Medicare Appeals Council will dismiss a late request for review unless you show that you had a good reason for not filing it on time.

How do I file an appeal?

To appeal, you must ask the Medicare Appeals Council to review the decision. Your appeal must be in writing, except that a request for expedited review of a Part D decision may be made orally as described below. Your appeal must identify the parts of the decision that you disagree with, and explain why you disagree.

You may submit a written request for review to the Medicare Appeals Council using one of three available methods: mail, fax, or electronic filing (E-File). **Please do not submit your request for review using more than one method.** Regardless of how you file your appeal, **you must always send a copy of your written request for review to the other parties who received a copy of the decision.**

If you are filing a written request for review, you may use the enclosed *Request for Review* (form DAB-101), or you may write a letter containing the following:

- The beneficiary's/enrollee's name (and telephone number for Part D appeals);
- The beneficiary's/enrollee's Medicare number (Health Insurance Claim Number or Medicare Beneficiary Identifier);
- The item(s), service(s), or specific Part D drug(s) in dispute;
- The specific date(s) the item(s) or service(s) were provided, if applicable;
- For Part D appeals, the plan name;
- For Part D appeals, the OMHA Appeal Number on the adjudicator's decision;
- For Part D appeals requesting expedited review, a statement that you are requesting expedited review;
- The date of the adjudicator's decision (not required for Part D appeals); and
- Your name and signature, and, if applicable, the name and signature of your representative.

Filing by mail:

Mail your appeal and a copy of the enclosed decision to:

Department of Health and Human Services
Departmental Appeals Board
Medicare Appeals Council, MS 6127
Cohen Building Room G-644
330 Independence Ave., S.W.
Washington, D.C. 20201

Filing by fax:

Fax your appeal and a copy of the enclosed decision to **(202) 565-0227**.

Filing by computer:

Using your web browser, visit the Medicare Operations Division Electronic Filing System (MOD E-File) website at <https://dab.efile.hhs.gov/mod>.

To file a new appeal using MOD E-File, you will need to register by:

- (1) Clicking **Register** on the MOD E-File home page;
- (2) Entering the information requested on the "Register New Account" form; and
- (3) Clicking **Register Account** at the bottom of the form.

You will use the email address and password you provided during registration to access MOD E-File at <https://dab.efile.hhs.gov/mod/users/new>. You will be able to use MOD E-File to file and access the specific materials for appeals to which you are a party or a party's representative. You may check the status of any appeal on the website homepage without registering.

Once registered, you may file your appeal by:

- (1) Logging into MOD E-File;
- (2) Clicking the **File New Appeal** menu button on the top right of the screen;
- (3) Selecting the type of appeal you are filing (Request for Review or Request for Escalation); and
- (4) Entering the requested Appeal Information and uploading the requested Appeal Documents on the "File New Appeal – Medicare Operations Division" form. You are required to provide information and documents marked with an asterisk.

At a minimum, the Medicare Appeals Council requires an appellant to file a signed Request for Review and a copy of the enclosed decision. All documents should be submitted in Portable Document Format (PDF) whenever possible. Any document, including a Request for Review, will be deemed to have been filed on a given day, if it is uploaded to MOD E-File on or before 11:59 p.m. EST of that day.

Currently, the documents that may be filed electronically are the:

- (1) Request for Review;
- (2) Appointment of Representative form (OMB Form 0938-0950);
- (3) Copy of Administrative Law Judge or attorney adjudicator decision;
- (4) Memorandum or brief or other written statement in support of your appeal; and
- (5) Request to Withdraw your appeal

No other documents aside from the five (5) listed categories above may be submitted through MOD E-File.

Filing by oral request (for expedited review only):

Oral requests for expedited review of a Part D decision may be made by telephone to (866) 365-8204. You must provide the information listed in the bullet points above and a statement that you are requesting an expedited review within 60 calendar days after receipt of this notice of

decision. The Medicare Appeals Council will document the oral request in writing and maintain the documentation in the case file.

Please note that your request for review will only be expedited if (1) the appeal involves an issue specified in 42 C.F.R. § 423.566(b), but does not include solely a request for payment of a Part D drug that has already been furnished, and (2) the prescribing physician (or other prescriber) indicates, or the Medicare Appeals Council determines, that the standard time frame may seriously jeopardize your life, health, or ability to regain maximum function.

How will the Medicare Appeals Council respond to my appeal?

The Medicare Appeals Council will limit its review to the issues raised in the appeal, unless the appeal is filed by an unrepresented beneficiary/enrollee. It may change the parts of the decision that you agree with. It may adopt, modify, or reverse the decision, in whole or in part, or it may send the case back to OMHA for further action. It may also dismiss your appeal.

Questions?

You may call or write our office. A toll-free phone number and mailing address are at the top of this notice.

Additional information about filing an appeal with the Medicare Appeals Council is available at <http://www.hhs.gov/dab/>. You can also call the Medicare Appeals Council's staff in the Medicare Operations Division of the Departmental Appeals Board at (202) 565-0100 or (866) 365-8204 (toll free), if you have questions about filing an appeal.

cc:

D. Christenson
5754 Clevedon Lane
Oshkosh, WI 54904-9729

C2C Innovative Solutions, Inc.
DME QIC Appeals-ALJ
P.O. Box 44006
Jacksonville, FL 32231-4006

Novocure, Inc.
195 Commerce Way
Portsmouth, NH 03801

Enclosures:

OMHA-152, Decision
DAB-101, Request for Review



Department of Health and Human Services
OFFICE OF MEDICARE HEARINGS AND APPEALS
Cleveland Field Office
Cleveland, Ohio

| | |
|------------------------------------|-----------------------------------------------------------------|
| Appeal of: D. Christenson | ALJ Appeal No.: 1-8285652321 |
| Beneficiary: D. Christenson | Medicare Part B |
| HICN: *****3639A | Before: Thomas S. Tyler U.S. Administrative Law Judge |

DECISION

After carefully considering the evidence and arguments presented in the record, a **FULLY FAVORABLE** on-the-record decision is entered for the Beneficiary.

Procedural History

Novocure, Inc., the provider, submitted claims to Medicare for tumor treatment field therapy (TTFT), electric stimulation cancer treatment (E0766) it provided to the Beneficiary from January 3, 2018 to April 3, 2018. The claims were denied initially and upon reconsideration. The matter was then forwarded to C2C Solutions, Inc., a qualified independent contractor (QIC), which issued an unfavorable decision on December 27, 2018 and found the provider liable for payment of the non-covered services.

The Office of Medicare Hearings and Appeals (OMHA) received the Appellant's timely filed appeal. The remaining amount in controversy meets the jurisdictional requirements for a hearing before OMHA.

A telephone hearing in this matter was scheduled to be held on March 28, 2019 at 1:30 PM EST in Cleveland, Ohio before the undersigned ALJ. However, because all of the issues have been resolved in the Beneficiary's favor, a hearing was not conducted and a decision on-the-record has been entered pursuant to 42 C.F.R. §405.1000(g). All exhibits were entered into the record as evidence.

Issue

The issue is whether the tumor treatment field therapy (TTFT) provided to the Beneficiary from January 3, 2018 to April 3, 2018 is covered under Medicare Part B.

Findings of Fact

The Beneficiary in this case is a 65 year-old man who was diagnosed with glioblastoma (GBM) in July 2015. Specifically, he had a right occipital brain tumor. He had surgery and was treated with chemotherapy and radiation. Thereafter, his physician prescribed the tumor treatment field therapy (TTFT). The TTFT is durable medical equipment that delivers alternating electric fields or tumor treating fields to the brain. The device consists of an electric field generator which is connected to four insulated transducer arrays. The arrays are placed on the patients scalp and deliver the tumor treating fields therapy in order to interfere with the growth of the patient's glioblastoma tumors. (Exhibit 2; Beneficiary's Pre-hearing Brief).

The physician signed a renewal prescription form for Optune on November 29, 2017. (Exhibit 2, p. 56). NOVO-TTF transducers were delivered to the Beneficiary on January 3, 2018, February 3, 2018, March 3, 2018 and April 3, 2018. (*Id.* at pp. 52-55).

The record contains multiple articles regarding the efficacy of the use of Optune for the treatment of both initially discovered and recurring glioblastoma. (Exhibit 1). The following historic information is identified in the documentation:

In April 2011, the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) approved commercial distribution of the Optune device for treatment of adult patients (22 years of age and older) with histologically-confirmed glioblastoma multiforme (GBM) following histologically- or radiologically- confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. In the pre-market approval letter, CDRH noted the device was intended to be used as a monotherapy, and was intended as an alternative to standard medical therapy for GBM after surgical and radiation options had been exhausted.

In October 2015, the CDRH issued a pre-market approval supplement for Optune. The supplement approved Optune as a treatment for adult patients (22 years of age or older) with histologically-confirmed GBM and Optune with temozolomide for the treatment of adult patients with newly diagnosed, supranentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant chemotherapy.

In 2018, the National Comprehensive Cancer Network (NCCN) Guidelines (version 1.2018; March 20, 2018) were updated to include alternating electric field therapy (TTFT) as an NCCN category I recommendation following post-operative standard brain radiation therapy with concurrent temozolomide. (See CD, file "NCCN_CNS_2018.pdf"). (Exhibit 3).

Peer-reviewed literature suggests that tumor-treating fields, also known as alternating electric fields, disrupt the cell division process in cancerous tumors which may lead to programmed cell death, or apoptosis. Tumor treating fields have shown statistically significant improvement in patient survival and outcomes in GBM brain tumors compared with traditional standards of care alone. (Exh. 2, pp. 49-79; *See also*, CD, Optune Peer Reviewed Literature; *Hearing Record*).

A large number of health care insurance providers have medical policies in place allowing coverage for Optune for the treatment of glioblastoma multiforme when certain conditions are met. These providers include, but are not limited to AETNA, Highmark, Anthem, Humana, Kaiser, United Healthcare, Cigna, Geisinger, and Blue Cross Blue Shield. (See CD, Optune Medical Policies November 2018; *Hearing Record*).

Legal Framework

I. ALJ Review Authority

A. Jurisdiction

An individual who, or an organization that, is dissatisfied with the reconsideration of an initial determination is entitled to a hearing before the Secretary of the Department of Health and Human Services (HHS), provided there is a sufficient amount in controversy and a request for hearing is filed in a timely manner. Social Security Act (Act) § 1869(b)(1)(A).

In implementing this statutory directive, the Secretary has delegated the authority to administer the nationwide hearings and appeals system for the Medicare program to OMHA. See 70 Fed. Reg. 36386, 36387 (June 23, 2005). The ALJs within OMHA issue the final decisions of the Secretary, except for decisions reviewed by the Medicare Appeals Council. *Id.*

A hearing before an ALJ is only available if the remaining amount in controversy is \$160 or more. See 76 Fed. Reg. 59138 (Sept. 23, 2011) and 42 C.F.R. §405.1006(b)(2). The request for hearing is timely if filed within sixty days from the date the party receives notice of the QIC's reconsideration. See 42 C.F.R. § 405.1014(b)(1).

B. Scope of Review

Under the implementation policy of the Centers for Medicare and Medicaid Services, United States Department of Health and Human Services, all appeal requests stemming from a QIC reconsideration are governed by the Administrative Law Judge Hearing Procedures outlined in 42 C.F.R. §§ 405.1000 – 1018. 70 Fed. Reg. 11425 (March 8, 2005).

The issues before the administrative law judge include all the issues brought out in the initial determination, redetermination, or reconsideration that were not decided entirely in the party's favor. However, if evidence presented before the hearing causes the administrative law judge to question a favorable portion of the determination, the administrative law judge will notify the parties before the hearing and may consider it an issue at the hearing. 42 C.F.R. § 405.1032(a).

C. Standard of Review

The Office of Medicare Hearings and Appeals is staffed with Administrative Law Judges who conduct de novo hearings. 42 C.F.R. § 405.1000(d).

II. Principles of Law

A. Statutes and Regulations

The Medicare program, Title XVIII of the Social Security Act (the Act), is administered through the Centers for Medicare and Medicaid Services (CMS), a component of the United States Department of Health and Human Services (HHS). Under the authority of Section 1842(a) (1) (A) of the Act, the Secretary of HHS is authorized to enter into contracts with private entities for the day-to-day operations of the program.

Part B of Title XVIII, the Supplementary Medical Insurance program, provides coverage for a variety of medical services and supplies furnished by physicians, or by others in connection with physicians' services, for outpatient hospital services, and for a number of other specific health-related items and services. Individuals participate voluntarily in the Medicare Part B program and pay a monthly premium.

Sections 1832(a)(2)(B), 1861(s)(6), and 1862(a)(1)(A) of the Act provide that Part B covers durable medical equipment (DME) that is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.

Title XVIII, § 1833(e) of the Act provides that no payment shall be made to any provider of services or other person under this part unless there has been furnished such information as may be necessary in order to determine the amounts due such provider or other person under this part for the period with respect to which the amounts are being paid or for any prior period.

B. Medicare Manual System

Administrative Law Judges may also give consideration to the manuals and rulings issued by the CMS in determining benefit coverage and eligibility. Although not binding on the Administrative Law Judge, the respective manuals provide guidance in the administration of the Medicare program. (*Shalala v. Guernsey Memorial Hospital*, 514 U.S. 87 (1995)).

Section 1871(a)(2) of the Act provides that no rule, requirement or statement of policy, other than a National Coverage Determination ("NCD"), can establish or change a substantive legal standard governing the scope of benefits or payment for services under the Medicare program unless it is promulgated as a regulation by CMS. However, although not subject to the force and effect of the law, CMS and its contractors, have issued policy and guidelines, including Local Coverage Determinations (LCD's) that describe criteria for coverage for selected types of medical services and supplies. NCDs promulgated by the Secretary of HHS under the authority of § 1862(a)(1) of the Act dictate the criteria under which specified services, procedures or supplies are covered by Medicare. NCDs are binding upon ALJs. 42 CFR §405.732(a)(4). "An ALJ may not disregard, set aside or otherwise review an NCD." (42 CFR §405.732(b)(1)).

There is no NCD specific to tumor treatment field therapy. However, there is a local coverage determination that can be found at L34823. Local Coverage Determination, L34823 addresses tumor treatment field therapy (TTFT). It states:

For any item to be covered by Medicare, it must 1) be eligible for a defined Medicare benefit category, 2) be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member, and 3) meet all other applicable Medicare statutory and regulatory requirements. For the items addressed in this local coverage determination, the criteria for "reasonable and necessary", based on Social Security Act § 1862(a)(1)(A) provisions, are defined by the following coverage indications, limitations and/or medical necessity.

For an item to be covered by Medicare, a detailed written order (DWO) must be received by the supplier before a claim is submitted. If the supplier bills for an item addressed in this policy without first receiving the completed DWO, the item will be denied as not reasonable and necessary.

Tumor treatment field therapy (E0766) will be denied as not reasonable and necessary.

A4555 ELECTRODE/TRANSDUCER FOR USE WITH ELECTRICAL STIMULATION DEVICE USED FOR CANCER TREATMENT, REPLACEMENT ONLY

E0766 ELECTRICAL STIMULATION DEVICE USED FOR CANCER TREATMENT, INCLUDES ALL ACCESSORIES, ANY TYPE

Policy article A52711 that supplements the LCD provides that "Tumor treatment field therapy devices are covered under the Durable Medical Equipment benefit (Social Security Act §1861(s)(6)). In order for a beneficiary's equipment to be eligible for reimbursement the reasonable and necessary (R&N) requirements set out in the related Local Coverage Determination must be met. In addition, there are specific statutory payment policy requirements, discussed below, that also must be met."

Further, the Policy Article States that "Code E0766 is in the frequent and substantial service payment category. Items included in this payment category are reimbursed a single monthly fee schedule amount for the device and all related supplies and accessories. Separate billing of supplies and/or accessories will be denied as unbundling."

Analysis

At issue in this case is whether reimbursement can be made for the TTFT therapy provided to the Beneficiary in four monthly applications from January 3, 2018 to April 3, 2018.

The Local Coverage Determination that addresses TTField therapy, L34823, specifically denies coverage. It states that tumor treatment field therapy (E0766) will be denied as not reasonable and

necessary. The LCD does not provide any circumstances under which TTField therapy would be covered.

The Beneficiary in this case has glioblastoma and was given a prescription by his treating physician to use TTField therapy following resection, radiation and chemotherapy. The Beneficiary, through his counsel, stated that he understands that there is an LCD that states that TTField therapy is not medically reasonable and necessary but notes that the last revision of the LCD L34832 was in 2013. The Beneficiary explained that the Optune therapy system that is at issue in this case was FDA approved for treatment of glioblastoma in 2015.

While we acknowledge that Medicare appropriately considered LCD L34832 in making the decision to deny the TTField therapy in this case based upon the unambiguous pronouncement that "tumor treatment field therapy (E0766) will be denied as not reasonable and necessary," we decline to follow that statement in the LCD. The Code of Federal Regulations identify the applicability of Local Coverage Determinations. It states that LCDs are required to be adhered to by Medicare contractors. (42 C.F.R. §405.1062). However, Administrative Law Judges and the Medicare Appeals Council are not bound by LCDs. If an ALJ declines to follow an LCD in a particular case, he or she may do so, but must explain why the policy was not followed. (*Id.*).

LCD L34832 does specifically state that TTField therapy will be denied as not reasonable and necessary. The tumor treatment field therapy that the Appellant is seeking is called "Optune." "Optune is a portable battery or power supply operated device which produces alternating electrical fields, called tumor treatment fields (TTFields) within the human body. The TTFields are applied to the patient's shaved head by means of electrically insulated surface transducer arrays, such that resistively coupled electric currents are not delivered to the patient. The TTFields disrupt the rapid cell division exhibited by cancer cells." https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034S013b.pdf. The peer-reviewed literature shows that tumor treating fields disrupt the cell division process in cancerous tumors which may lead to programmed cell death. Tumor treating fields have also shown statistically significant improvement in patient survival rates and outcomes in GBM brain tumors when compared with the traditional standard of care alone. While we acknowledge that the QIC appropriately considered LCD L34823 in making the decision to deny the Optune treatment in this case based upon the unambiguous pronouncement that the type of treatment is not reasonable and necessary, we feel we must decline to follow that statement in the LCD. No explanation was provided by the LCD for the failure to cover the TTField therapy. Certainly, the LCD is not required to include reasons for the denial of non-covered services. However, in giving an LCD its required deference when considering whether to abide by a pronouncement that is not binding on an ALJ, the reason for the non-coverage would be helpful to assess the applicability of the LCD. Here, we cannot determine the reasons for non-coverage but find that the rationales for finding coverage are extensive. In exercising our review authority, we hereby provide the bases for why we decline to follow the pronouncement in the LCD. (42 C.F.R. §405.1062(a)).

Without an explanation in the LCD as to why TTF therapy is considered as not medically reasonable and necessary, we are left to speculate. The TTFT was likely an emerging technology that had not been widely reviewed or tested for medical efficacy at the time the language was included in the LCD limiting its coverage. However, Optune was approved by the FDA for use in

the treatment of newly diagnosed glioblastoma on October 5, 2015¹. Moreover, at around the same time of the last LCD update, there were studies conducted and the results published passing on the efficacy of the use of TTField therapy, most notably the Optune (NovoTTF-100A therapy), for recurrent and new diagnoses of glioblastoma. *Stupp et al., NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomized phase III trial of a novel treatment modality*. Eur J Cancer. 2012 Sep; 48(14):2192-202. The results of further studies were presented in the Annual Meeting of the American Association for Cancer Research. *Stupp, Hegi, Idbaih, et al. Tumor treating fields added to standard chemotherapy in newly diagnosed glioblastoma (GBM): final results of a randomized, multicenter phase III trial*, Program and Abstracts of the 2017 Annual Meeting of the American Association for Cancer Research April 1-April 5, 2017 Washington, D.C. Abstract LBA AACR CT007. The results of these studies determined that Optune in combination with temozolomide was an effective treatment of this particular brain cancer, whether newly diagnosed or recurrent, that resulted in significant improvement in life expectancy of most patients.

We are also persuaded by the Beneficiary's medical provider. The Beneficiary's physician prescribed the treatment at issue in this case based upon the numerous studies and articles that described the medical effectiveness of Optune and based upon his own experience with the treatment.

On the basis of the foregoing, we decline to follow the LCD. The FDA approval of Optune, the overwhelming medical research evidence and the medical notes of the Beneficiary's physician discloses that Optune is effective in extending the lives of patients who have been newly diagnosed or have recurrent glioblastoma. We do not fault Medicare contractors for coming to a different conclusion. They adhered to the pronouncement in the LCD. However, if ever there was a reason for an ALJ to vary from the strict, unexplained pronouncement in an LCD, it is this case where the very life of the Beneficiary holds in the balance, with very few, if any, other medical options to treat him and prolong his life aside from the treatment provided by the Optune device.

Consequently, the undersigned finds that the Medicare requirements have been met. Accordingly, the ALJ finds that the TTFT treatment provided to the Beneficiary in this case are covered under Medicare Part B.

Conclusions of Law

Based on the foregoing, the undersigned concludes as a matter of law that the Optune Tumor Treatment Field Therapy services were shown to be medically reasonable and necessary and are covered under Medicare. The Beneficiary is entitled to reimbursement of the costs billed.

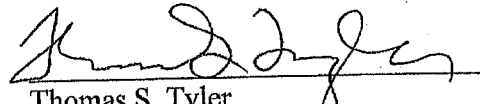
¹ https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034S013b.pdf

Order

The Medicare Contractor is **DIRECTED** to process the claim in accordance with this decision.

SO ORDERED.

Dated: 4/2/19


Thomas S. Tyler
U.S. Administrative Law Judge



Department of Health and Human Services
Office of the Secretary

19-137
19-138

OFFICE OF MEDICARE HEARINGS AND APPEALS

Cleveland Field Office
200 Public Square, Suite 1300
Cleveland, OH 44114-2316
216-615-4000 (Main)
216-615-7548 (ALJ Zettel Team)
216-615-4108 (Fax)
866-236-6089 (Toll Free)

Date: JUNE 6, 2019

DEBRA PARRISH, ESQ.
PARRISH LAW OFFICES
788 WASHINGTON ROAD
PITTSBURGH, PA 15228

NOTICE OF DECISION

Appellant: D. CHRISTENSON
OMHA Appeal Number: 1-8416229632 & 1-8416270832

Enclosed is the decision for the above case. This decision is based on the administrative record, including any evidence or testimony presented at the hearing, if one was held. The decision is not precedential, does not release the appellant from civil or criminal liability, and may be reopened at any time if it was procured by fraud or similar fault. In addition, the decision may be reopened within 180 calendar days from the date of the decision for good cause. Good cause exists when there is new and material evidence that was not available or known at the time of the decision and may result in a different conclusion, or when the evidence that was considered clearly shows on its face that an obvious error was made at the time of the decision.

What if I disagree with the decision?

If you disagree with the decision, you may file an appeal with the Medicare Appeals Council. Other parties may also appeal the decision. In addition, the Medicare Appeals Council may decide to review the decision on its own motion. If no party appeals the decision and the Medicare Appeals Council does not review the decision, the decision is binding on all parties and you and the other parties will not have the right to ask a federal court to review the decision.

If you are not already represented, you may appoint an attorney or other person to represent you.

How much time do I have to file an appeal?

The Medicare Appeals Council must receive your written appeal within 60 calendar days of the date that you receive this notice. The Medicare Appeals Council assumes you received this notice 5 calendar days after the date of the notice unless you show that you did not receive it within the 5-day period.

The Medicare Appeals Council will dismiss a late request for review unless you show that you had a good reason for not filing it on time.

How do I file an appeal?

To appeal, you must ask the Medicare Appeals Council to review the decision. Your appeal must be in writing, except that a request for expedited review of a Part D decision may be made orally as described below. Your appeal must identify the parts of the decision that you disagree with, and explain why you disagree.

You may submit a written request for review to the Medicare Appeals Council using one of three available methods: mail, fax, or electronic filing (E-File). **Please do not submit your request for review using more than one method.** Regardless of how you file your appeal, you must always send a copy of your written request for review to the other parties who received a copy of the decision.

If you are filing a written request for review, you may use the enclosed *Request for Review* (form DAB-101), or you may write a letter containing the following:

- The beneficiary's/enrollee's name (and telephone number for Part D appeals);
- The beneficiary's/enrollee's Medicare number (Health Insurance Claim Number or Medicare Beneficiary Identifier);
- The item(s), service(s), or specific Part D drug(s) in dispute;
- The specific date(s) the item(s) or service(s) were provided, if applicable;
- For Part D appeals, the plan name;
- For Part D appeals, the OMHA Appeal Number on the adjudicator's decision;
- For Part D appeals requesting expedited review, a statement that you are requesting expedited review;
- The date of the adjudicator's decision (not required for Part D appeals); and
- Your name and signature, and, if applicable, the name and signature of your representative.

Filing by mail:

Mail your appeal and a copy of the enclosed decision to:

Department of Health and Human Services
Departmental Appeals Board
Medicare Appeals Council, MS 6127
Cohen Building Room G-644
330 Independence Ave., S.W.
Washington, D.C. 20201

Filing by fax:

Fax your appeal and a copy of the enclosed decision to (202) 565-0227.

Filing by computer:

Using your web browser, visit the Medicare Operations Division Electronic Filing System (MOD E-File) website at <https://dab.efile.hhs.gov/mod>.

To file a new appeal using MOD E-File, you will need to register by:

- (1) Clicking **Register** on the MOD E-File home page;
- (2) Entering the information requested on the "Register New Account" form; and
- (3) Clicking **Register Account** at the bottom of the form.

You will use the email address and password you provided during registration to access MOD E-File at <https://dab.efile.hhs.gov/mod/users/new>. You will be able to use MOD E-File to file and access the specific materials for appeals to which you are a party or a party's representative. You may check the status of any appeal on the website homepage without registering.

Once registered, you may file your appeal by:

- (1) Logging into MOD E-File;
- (2) Clicking the **File New Appeal** menu button on the top right of the screen;
- (3) Selecting the type of appeal you are filing (Request for Review or Request for Escalation); and
- (4) Entering the requested Appeal Information and uploading the requested Appeal Documents on the "File New Appeal – Medicare Operations Division" form. You are required to provide information and documents marked with an asterisk.

At a minimum, the Medicare Appeals Council requires an appellant to file a signed Request for Review and a copy of the enclosed decision. All documents should be submitted in Portable Document Format (PDF) whenever possible. Any document, including a Request for Review, will be deemed to have been filed on a given day, if it is uploaded to MOD E-File on or before 11:59 p.m. EST of that day.

Currently, the documents that may be filed electronically are the:

- (1) Request for Review;
- (2) Appointment of Representative form (OMB Form 0938-0950);
- (3) Copy of Administrative Law Judge or attorney adjudicator decision;
- (4) Memorandum or brief or other written statement in support of your appeal; and
- (5) Request to Withdraw your appeal

No other documents aside from the five (5) listed categories above may be submitted through MOD E-File.

Filing by oral request (for expedited review only):

Oral requests for expedited review of a Part D decision may be made by telephone to (866) 365-8204. You must provide the information listed in the bullet points above and a statement that you are requesting an expedited review within 60 calendar days after receipt of this notice of

decision. The Medicare Appeals Council will document the oral request in writing and maintain the documentation in the case file.

Please note that your request for review will only be expedited if (1) the appeal involves an issue specified in 42 C.F.R. § 423.566(b), but does not include solely a request for payment of a Part D drug that has already been furnished, and (2) the prescribing physician (or other prescriber) indicates, or the Medicare Appeals Council determines, that the standard time frame may seriously jeopardize your life, health, or ability to regain maximum function.

How will the Medicare Appeals Council respond to my appeal?

The Medicare Appeals Council will limit its review to the issues raised in the appeal, unless the appeal is filed by an unrepresented beneficiary/enrollee. It may change the parts of the decision that you agree with. It may adopt, modify, or reverse the decision, in whole or in part, or it may send the case back to OMHA for further action. It may also dismiss your appeal.

Questions?

You may call or write our office. A toll-free phone number and mailing address are at the top of this notice.

Additional information about filing an appeal with the Medicare Appeals Council is available at <http://www.hhs.gov/dab/>. You can also call the Medicare Appeals Council's staff in the Medicare Operations Division of the Departmental Appeals Board at (202) 565-0100 or (866) 365-8204 (toll free), if you have questions about filing an appeal.

cc:

D. CHRISTENSON
5754 CLEVEDON LN
OSHKOSH, WI 54904-9729

C2C Innovative Solutions, Inc.
DME QIC Appeals-ALJ
P.O. Box 44006
Jacksonville, FL 32231-4006

NOVOCURE INC.
195 Commerce Way
Portsmouth, NH 03801

Enclosures:

OMHA-152, Decision
DAB-101, Request for Review



Department of Health and Human Services
OFFICE OF MEDICARE HEARINGS AND APPEALS
Cleveland, Ohio

| | | |
|---------------|----------------|------------------------------------------------------------|
| Appeal of: | D. Christenson | OMHA Appeal No.: 1-8416270832 1-8416229632 |
| Beneficiary: | D. Christenson | Medicare Part B |
| Medicare No.: | *****3639A | Before: Richard J. Zettel U.S. Administrative Law Judge |

DECISION

After carefully considering the evidence and arguments presented in the record and at the hearing, a **FULLY FAVORABLE** decision is entered for the Appellant, D. Christenson.

Procedural History

The Appellant was treated with electronic stimulation cancer treatment, tumor treatment field therapy (CPT code E0766) (hereinafter referred to as "TTFT") on a monthly basis from May 3, 2018, through October 3, 2018 (Exhibit 2). *See*, Attachment A. The Provider of the TTFT was Novocure Inc. Claims for the TTFT were submitted to a Part B Durable Medical Equipment Medicare Administrative Contractor (DME MAC), which were denied initially and upon redetermination (Exhibit 1). On March 12, 2019, and March 19, 2019, a Qualified Independent Contractor (QIC), C2C Solutions, Inc., issued unfavorable reconsideration decisions (Exhibit 1, page 1). The QIC determined that LCD L34823 details that TTFT will be denied as not reasonable and necessary. The QIC held the Provider liable for the non-covered charges.

On March 29, 2019, the Appellant submitted timely requests for an Administrative Law Judge (ALJ) hearing to the Office of Medicare Hearings and Appeals (OMHA) (Exhibit 3, pages 5 and 1). On April 19, 2019, the Provider submitted a request for an ALJ hearing to the OMHA (Exhibit 3, pages 1 and 14). The amount in controversy meets the jurisdictional requirement for a hearing before OMHA in each appeal (Exhibit 1).

A telephonic hearing before the ALJ was held on May 15, 2019, in Cleveland, Ohio. Debra Parrish, Esq. appeared on behalf of the Appellant. Julie Miles, RN, Clinical Appeals Specialist,

appeared on behalf of the Appellant and testified under oath. Exhibits 1-4 were admitted into the record in each appeal.

Issues

The ALJ is asked to decide whether the TTFT provided to the Appellant on multiple dates of service is reimbursable under Part B of Title XVIII of the Social Security Act, and if not, who is liable for the non-covered charges.

Findings of Fact

The attached Exhibit List is incorporated into this Decision by reference. The following facts are established by the preponderance of the evidence.

1. The Appellant was treated with electronic stimulation cancer treatment, tumor treatment field therapy (CPT code E0766) (hereinafter referred to as "TTFT") (also known as "Optune") on a monthly basis from May 3, 2018, through October 3, 2018 (Exhibit 2). *See*, Attachment A.
2. The Appellant was 63 years-old during the dates of service at issue (Exhibit 2, page 1).¹
3. On July 20, 2015, the Appellant underwent a right parietal occipital craniectomy (Exhibit 2, page 48). The biopsies of the right occipital brain tumor showed high grade glial tumor consistent
4. The record of the appeal includes office notes documenting the Appellant's treatment for glioblastoma multiforme, including surgery, radiation, and chemotherapy (Exhibit 2).
5. The Appellant received primary therapy with temozolomide and external beam radiation therapy (*Id.* and Exhibit 2, page 6). He had recurrence in the surgical bed roughly four months later and was treated with radiosurgery.
6. In 2016, the Appellant began using Optune therapy. *Id.* Since that time through September 19, 2018, the Appellant had been stable, if not improved in his imaging.
7. On September 18, 2018, an MRI of the brain revealed the following: stable postoperative findings of right craniotomy for right occipital tumor resection with unchanged appearance of the heterogeneously enhancing resection cavity; no evidence of tumor progression; flair hyperintense signal surround the resection cavity and extending throughout the right cerebral hemisphere; and unchanged mass effect with 4 mm midline shift to the left (Exhibit 2, page 8).
8. The plan was for the Appellant to continue on Optune therapy indefinitely (Exhibit 2, page 6).

¹ Exhibit numbers refer to OMHA Appeal No. 1-8416229632 unless otherwise specified.

9. Page two of three of the Optune Prescription Form was signed by the Appellant on September 22, 2016 (Exhibit 2, page 3).
10. Page one of five of the Optune Prescription Form was signed by the physician on November 29, 2017 (Exhibit 2, page 2). The prescription provides that the Beneficiary had a diagnosis of glioblastoma multiforme. The prescription provides that it was a renewal.
11. Page one of five of the Optune Prescription Form was signed by the physician on May 16, 2018 (Exhibit 2, page 1). The prescription provides that the Beneficiary had a diagnosis of recurrent GBM (glioblastoma multiforme).
12. Optune is FDA approved for recurrent and newly diagnosed glioblastoma multiforme brain tumors (Exhibit 4, page 7; Hearing testimony).
13. TTFT disrupts and corrupts the division of cancer cells and leads to the death of such cells. *Id.*
14. Peer-reviewed literature shows the improved clinical outcome of patients who receive TTFT for their glioblastoma (Exhibit 1 (both appeals); Hearing testimony).
15. TTFT for glioblastoma is included in the National Comprehensive Cancer Network (NCCN) guidelines (Exhibit 1, page 46). The NCCN guidelines for recurrent glioblastoma include "consider alternate electric field therapy for glioblastoma (Category 2B)."

Legal Framework

I. ALJ Review Authority

A. Jurisdiction

An individual who, or an organization that, is dissatisfied with the reconsideration of an initial determination is entitled to a hearing before the Secretary of the Department of Health and Human Services (HHS), provided there is a sufficient amount in controversy and a request for hearing is filed in a timely manner. Social Security Act (Act) § 1869(b)(1)(A).

In implementing this statutory directive, the Secretary has delegated the authority to administer the nationwide hearings and appeals system for the Medicare program to OMHA. The ALJs within OMHA issue the final decisions of the Secretary, except for decisions reviewed by the Medicare Appeals Council.

A hearing before an ALJ is only available if the remaining amount in controversy is \$160. 83 Fed. Reg. 47619 (Sept. 20, 2018) (setting the 2019 amount in controversy threshold amount at \$160). The request for hearing is timely if filed within sixty days after receipt of the QIC's reconsideration decision. *See*, 42 C.F.R. § 405.1002.

B. Scope of Review

"The issues before the ALJ include all the issues brought out in the initial determination, redetermination, or reconsideration that were not decided entirely in a party's favor. (For purposes of this provision, the term "party" does not include a representative of CMS or one of its contractors that may be participating in the hearing.) However, if evidence presented before the hearing causes the ALJ to question a favorable portion of the determination, he or she notifies the parties before the hearing and may consider it an issue at the hearing." *See*, 42 C.F.R. § 405.1032(a).

C. Standard of Review

Pursuant to § 557 of the Administrative Procedure Act ("APA"), an ALJ qualified and appointed pursuant to the APA acts as an independent finder of fact in conducting a hearing pursuant to § 1869 of the Act. The ALJ conducts a de novo review and issues a decision based on the hearing record. 42 C.F.R. § 405.1000(d).

II. Principles of Law

A. Social Security Act and Code of Federal Regulations

The Medicare program, Title XVIII of the Act, is administered through the Centers for Medicare and Medicaid Services, a component of the United States Department of Health and Human Services (HHS). Under the authority of Section 1842(a) (1) (A) of the Act, the Secretary of HHS is authorized to enter into contracts with private entities for the day-to-day operations of the program. For claims for durable medical equipment, prosthetics, orthotics, and supplies, DME MACs administer the processing of the claims.

Part B of Title XVIII of the Act, the Supplementary Medical Insurance program, provides coverage for a variety of medical services and supplies furnished by physicians, or by others in connection with physicians' services, for outpatient hospital services, and for a number of other specific health-related items and services. Individuals participate voluntarily in the Medicare Part B program and pay a monthly premium.

Section 1862(a)(1) of the Act excludes Medicare payment for services which "are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member".

Section 1834(a)(15)(C) of the Act provides that carriers shall, at the request of a supplier or beneficiary, determine in advance of delivery of an item whether payment for the item may not be made because the item is not covered if the item is a customized item, the patient to whom the item is to be furnished, or the supplier, requests that such advance determination be made, and the item is not an inexpensive item as specified by the Secretary.

Section 1832(a) of the Act states, in pertinent part: The benefits provided to an individual by the insurance program established by this part shall consist of

- (1) entitlement to have payment made to him or on his behalf (subject to the provisions of this part) for medical or other health services...

Section 1861(s) of the Act provides that the term "medical and other health services" includes durable medical equipment. 42 CFR § 414.202 defines durable medical equipment as equipment furnished by a supplier or a home health agency that-

- (1) can withstand repeated use;
- (2) is primarily and customarily used to serve a medical purpose;
- (3) generally is not useful to an individual in the absence of an illness or injury;
and
- (4) is appropriate for use in the home.

42 CFR § 410.38(a) provides in pertinent part as follows regarding the scope and conditions of durable medical equipment:

Medicare Part B pays for the rental or purchase of durable medical equipment, including iron lungs, oxygen tents, hospital beds, and wheelchairs, if the equipment is used in the patient's home or in an institution that is used as a home.

B. CMS Manual System and Local Policy

The manuals issued by the Centers for Medicare and Medicaid Services (CMS) administering the Medicare program also are considered. Although not binding on the ALJ, the respective manuals provide guidance in the administration of the Medicare program. In *Shalala v. Guernsey Memorial Hospital*, 514 U.S. 87, 102 (1995), the United States Supreme Court concluded that an agency manual section is a valid interpretive rule and that it is reasonable for the agency to follow it. CMS, *Medicare Benefit Policy Manual (MBPM) (Internet-Only Manual Publ'n 100-2)* ch. 15, § 110, provides general coverage guidelines for durable medical equipment.

CMS, *Medicare Program Integrity Manual (MPIM) (Internet-Only Manual Publ'n 100-8)* ch. 13, § 13.5.1 includes the follow guidance for contractors when drafting a proposed Local Coverage Determination (LCD):

In order to be covered under Medicare, a service shall be reasonable and necessary. When appropriate, contractors shall describe the circumstances under which the proposed LCD for the service is considered reasonable and necessary under 1862(a)(1)(A). Contractors shall consider a service to be reasonable and necessary if the contractor determines that the service is:

- Safe and effective;
- Not experimental or investigational (exception: routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary); and
- Appropriate, including the duration and frequency that is considered appropriate for the service, in terms of whether it is:
 - o Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;

- o Furnished in a setting appropriate to the patient's medical needs and condition;
- o Ordered and furnished by qualified personnel;
- o One that meets, but does not exceed, the patient's medical need; and
- o At least as beneficial as an existing and available medically appropriate alternative.

MPIM, supra ch. 13, § 13.7.1 continues as follows:

In order of preference, LCDs should be based on:

- Published authoritative evidence derived from definitive randomized clinical trials or other definitive studies, and
- General acceptance by the medical community (standard of practice), as supported by sound medical evidence based on:
 - o Scientific data or research studies published in peer-reviewed medical journals;
 - o Consensus of expert medical opinion (i.e., recognized authorities in the field); or
 - o Medical opinion derived from consultations with medical associations or other health care experts.

Acceptance by individual health care providers, or even a limited group of health care providers, normally does not indicate general acceptance by the medical community. Testimonials indicating such limited acceptance, and limited case studies distributed by sponsors with financial interest in the outcome, are not sufficient evidence of general acceptance by the medical community. The broad range of available evidence must be considered and its quality shall be evaluated before a conclusion is reached.

A Local Coverage Determination (LCD), as established by § 522 of the Benefits Improvement and Protection Act, is a decision by a fiscal intermediary or carrier whether to cover a particular service on an intermediary-wide or carrier-wide basis in accordance with § 1862(a)(1)(A) of the Act (i.e., a determination as to whether the service is reasonable and necessary). CGS Administrators and Noridian Healthcare Solutions, LLC issued Local Coverage Determination: Tumor Treatment Field Therapy (LCD L34823) (Jan. 2017), which provides in relevant part as follows: Tumor treatment field therapy (E0766) will be denied as not reasonable and necessary.

Analysis

The QIC determined that LCD L34823 details that TTFT will be denied as not reasonable and necessary. The QIC held the Provider liable for the non-covered charges. The Appellant argues that TTFT should be covered by Medicare. The ALJ disagrees with the findings of the QIC and determines that the TTFT provided to the Appellant is covered under Part B of Medicare.

Medicare is a defined benefit program, which means that it does not cover all available medical services and supplies. Medicare coverage is limited to those medical services and supplies identified by Congress, and by the Secretary of Health and Human Services and CMS in implementing Congressional directives. Medicare does not cover medical services that are not medically reasonable and necessary under § 1862(a)(1) of Act.

The QIC relied upon LCD L34823 to deny coverage for the TTFT for the Appellant. LCD L34823 provides that TTFT will be denied as not reasonable and necessary. Pursuant to 42 C.F.R. § 405.1062(a), an ALJ must give substantial deference to local coverage determinations. If an ALJ declines to follow a local coverage determination, the ALJ must explain the reason

why the policy was not followed in accordance with 42 C.F.R. § 405.1062(b). After careful consideration of the record and hearing testimony, the ALJ has decided to depart from LCD L34823 under the specific facts of this appeal.

First, the ALJ finds that LCD L34823 fails to identify any justification for the denial of all TTFT as not reasonable and necessary. Pursuant to *MPIM supra* ch. 13, §13.7.1, contractors shall consider a service to be reasonable and necessary if the contractor determines that the service is safe and effective. The record and hearing testimony support that TTFT is a safe and effective treatment of glioblastoma. Optune is FDA approved for recurrent and newly diagnosed glioblastoma multiforme brain tumors. TTFT disrupts and corrupts the division of cancer cells and leads to the death of such cells. Peer-reviewed literature shows the improved clinical outcome of patients who receive TTFT for their glioblastoma. TTFT for glioblastoma is included in the National Comprehensive Cancer Network guidelines. The NCCN guidelines for recurrent glioblastoma include "consider alternate electric field therapy for glioblastoma (Category 2B)." The Appellant pointed out that many payers are covering TTFT based on individual medical necessity review as well as published medical policy. *See*, Exhibits 1. Therefore, the ALJ will not afford substantial deference to LCD L34823 and concludes that TTFT is a safe and effective treatment of recurrent glioblastoma.

Second, the ALJ finds that the documentation and hearing testimony support that TTFT is medically reasonable and necessary to treat the Appellant. The Appellant was 63 years-old during the dates of service at issue. On July 20, 2015, the Appellant underwent a right parietal occipital craniectomy. The biopsies of the right occipital brain tumor showed high grade glial tumor consistent. The record of the appeal includes office notes documenting the Appellant's treatment for glioblastoma multiforme, including surgery, radiation, and chemotherapy. The Appellant received primary therapy with temozolomide and external beam radiation therapy. He had recurrence in the surgical bed roughly four months later and was treated with radiosurgery.

In 2016, the Appellant began using Optune therapy. Since that time through September 19, 2018, the Appellant had been stable, if not improved in his imaging. On September 18, 2018, an MRI of the brain revealed the following: stable postoperative findings of right craniotomy for right occipital tumor resection with unchanged appearance of the heterogeneously enhancing resection cavity; no evidence of tumor progression; flair hyperintense signal surround the resection cavity and extending throughout the right cerebral hemisphere; and unchanged mass effect with 4 mm midline shift to the left. The plan was for the Appellant to continue on Optune therapy indefinitely. Ms. Miles stated that the Appellant was diagnosed with brain cancer in July 2015 and was put on Optune. Ms. Miles said that the Appellant was still alive, which is phenomenal. Ms. Miles noted that the Appellant's compliance with therapy is excellent.

Based on the foregoing, the TTFT provided to the Appellant on the dates of service was medically reasonable and necessary. The TTFT provided to the Appellant from May 3, 2018, through October 3, 2018, is reimbursable under Part B of Medicare.

Conclusions of Law

The ALJ concludes that the TTFT provided to the Appellant on multiple dates of service was medically reasonable and necessary. Accordingly, the ALJ finds that the TTFT provided to the

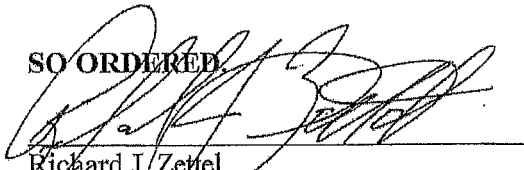
Appellant from May 3, 2018, through October 3, 2018, is reimbursable under Part B of Title XVIII of the Act. *See*, Attachment A.

Order

The Medicare Contractor is **DIRECTED** to process the claim in accordance with this decision.

Dated: June 6, 2019

SO ORDERED.


Richard J. Zetzel
U.S. Administrative Law Judge

Enclosures:

Form OMHA-156, *List of Exhibits*

ATTACHMENT A

| OMHA Appeal No. | Dates of Service |
|-----------------|--------------------------------------------------------|
| 1-8416229632 | May 3, 2018 June 3, 2018 July 3, 2018 |
| 1-8416270832 | August 3, 2018 September 3, 2018 October 3, 2018 |



Department of Health and Human Services
OFFICE OF MEDICARE HEARINGS AND APPEALS
Cleveland, Ohio

| | |
|------------------------------------|---------------------------------------------------------------------|
| Appeal of: D. CHRISTENSON | OMHA Appeal No.: 1-8416229632 |
| Beneficiary: D. CHRISTENSON | Medicare: Part B |
| Medicare No.: *****3639A | Before: Richard J. Zettel Administrative Law Judge |

EXHIBIT LIST

| EXHIBIT NUMBER | DESCRIPTION | PAGE NUMBERS |
|-------------------|-------------------------------------------------------------------|-----------------|
| 1 | Initial, Redetermination and Reconsideration Procedural Documents | 1-257 |
| 2 | Medical Records/Evidence Received by CMS Contractors | 1-97 |
| 3 | Request for ALJ Hearing | 1-17 |
| 4 | OMHA Proceedings | 1-21 |

Dated: 05.06.19



Department of Health and Human Services
OFFICE OF MEDICARE HEARINGS AND APPEALS
Cleveland, Ohio

| | |
|-----------------------------|-------------------------------------------------------|
| Appeal of: D. CHRISTENSON | OMHA Appeal No.: 1-8416270832 |
| Beneficiary: D. CHRISTENSON | Medicare: Part B |
| Medicare No.: *****3639A | Before: Richard J. Zettel Administrative Law Judge |

EXHIBIT LIST

| EXHIBIT NUMBER | DESCRIPTION | PAGE NUMBERS |
|-------------------|-------------------------------------------------------------------|-----------------|
| 1 | Initial, Redetermination and Reconsideration Procedural Documents | 1-1893 |
| 2 | Medical Records/Evidence Received by CMS Contractors | 1-50 |
| 3 | Request for ALJ Hearing | 1-12 |
| 4 | OMHA Proceedings | 1-21 |

Dated: 05.06.19

PARRISH LAW OFFICES

788 WASHINGTON ROAD
PITTSBURGH, PENNSYLVANIA 15228-2021
www.dparrishlaw.com

412.561.6250
FAX 412.561.6253
E-mail: info@dparrishlaw.com

September 18, 2019

VIA MOD E-FILE

Department of Health and Human Services
Departmental Appeals Board
Medicare Appeals Council, MS 6127
Cohen Building, Room G-644
330 Independence Ave., S.W.
Washington, D.C. 20201

Re: ALJ Appeal No.: 1-8630709341
Decision Date: September 12, 2019
Appellant/Beneficiary: D. Christenson
HICN: 7QR9QM0QP33
Service: E0766
Dates of Service: 11/3/2018; 12/3/2018; 1/3/2019
Our Ref.: 19-296

Dear Medicare Appeals Council:

David Christenson appeals the attached September 12, 2019 unfavorable decision by Administrative Law Judge Scott Watson with respect to the above-identified case. See Attachment 2. Appellant appeals the unfavorable portion of the decision based on mistake of fact and mistake of law.

I. The issues to be considered in the appeal are:

1. Did the ALJ make a mistake of law when he determined that LCDs are binding on ALJs?
2. Did the ALJ make a mistake of law when he failed to recognize and/or apply the principle of collateral estoppel?
3. Did the ALJ make a mistake of law when he applied an LCD that had been invalidated by operation of Medicare regulations?
4. Should the Appellant's request for coverage be granted?

II. Introduction

Mr. Christenson was prescribed an Optune system for his recurrent glioblastoma multiforme (GBM) (a kind of brain tumor) in early 2016. The Optune system delivers tumor treatment field therapy (TTFT). TTFT creates an electrical field that disrupts and corrupts the division of cancer cells and leads to the death of such cells. In 2011 and 2015, the FDA approved, through its more rigorous review process, the Optune device to deliver TTFT, finding it to be safe and effective for the treatment of glioblastomas. The initial FDA approval was for recurrent glioblastoma. The FDA then approved the Optune device for newly diagnosed glioblastomas. During the most recent clinical trial for glioblastomas (which included newly diagnosed and recurrent GBM), the interim TTFT results were so compelling (i.e., the treatment was able to show significant clinical benefit) that the Data Safety Monitoring Board recommended early termination of the study to enable patients not receiving the treatment to cross over and receive the treatment deeming it to be unethical to withhold TTFT from those not receiving it. The FDA agreed.

All the claims at issue were denied by the Medicare contractor citing LCD L34823 which simply states TTFT will be denied as not reasonable and necessary. The QIC denied the claims citing the LCD. Significantly, Medicare coverage for this beneficiary has been established. Two different Medicare ALJs determined that TTFT met Medicare coverage criteria for this beneficiary.

On July 18, 2019, the DMACs revised LCD L34823. When an LCD is revised after an LCD challenge is filed, that has the same effect as a judicial ruling that the LCD was invalid. See 42 C.F.R. §426.420(b). Nonetheless, the ALJ applied the old version of LCD L34823 and denied the claims asserting, "I am bound to follow Medicare rules and regulations." Decision at 4. No citation to any statute of regulation indicating that LCDs are binding on ALJ was provided. Further, the ALJ did not address any of the other issues raised, discuss the effect of the July 18, 2019 LCD revision, or the prior ALJ rulings. Although the ALJ conceded TTFT had been effective staving off for Mr. Christenson's otherwise fatal illness for over 3.5 year and had extended his life by seven-fold, the Judge Watson found no reason to deviate from the invalidated LCD. The decision reflects numerous errors of law and fact.

III. Errors of Law and Fact

Turning to the ALJ's decision, the ALJ denied coverage on the basis of LCD L34823. That was in error.

A. Collateral Estoppel

Medicare coverage of TTFT for Mr. Christenson repeatedly and explicitly has been found. See ALJ Nos. 1-8285652321 and 1-8416229632. These two prior favorable ALJ decisions are for other dates of service for the same device for the same condition which were

denied on the same basis. The Secretary is barred by the doctrine of collateral estoppel/issue preclusion from re-litigating those issues. As noted by a unanimous Supreme Court:

We have long favored application of the common-law doctrines of collateral estoppel (as to issues) and res judicata (as to claims) to those determinations of administrative bodies that have attained finality. When an administrative agency is acting in a judicial capacity and resolves dispute issues of fact properly before it which the parties have had an adequate opportunity to litigate, the courts have not hesitated to apply res judicata to enforce repose. Such repose is justified on the sound and obvious principle of judicial policy that a losing litigant deserves no rematch after a defeat fairly suffered, in adversarial proceedings, on an issue identical in substance to the one he subsequently seeks to raise. To hold otherwise would, as a general matter, impose unjustifiably upon those who have already shouldered their burdens, and drain the resources of an adjudicatory system with disputes resisting resolution. The principle holds true when a court has resolved an issue, and should do so equally when the issue has been decided by an administrative agency, be it state or federal, which acts in a judicial capacity.

See *Astoria Federal Savings and Loan Assoc. v. Solimino*, 501 U.S. 104, 107-8 (1991) (internal citations and quotations omitted). No basis exists for the Secretary to ignore the prior coverage rulings for this Medicare beneficiary. The ALJ did not even discuss the issue in his decision. Accordingly, coverage of Mr. Christenson's TTFT device should be ordered.

B. Failure to Comply With 42 C.F.R. § 405.1062(a)/(d)

As noted above, ALJs are not bound by LCDs and only give deference to them. See 42 C.F.R. § 405.1062(a). Further, ALJs are commanded to conduct a *de novo* review of the case. See 42 C.F.R. § 405.1062(d). Accordingly, there must be some fact(s) that a beneficiary could present that would cause the ALJ to not defer to an LCD. To hold otherwise would contradict the command of § 405.1062(a).

In the present case, Mr. Christenson presented evidence that, *after LCD L34823 issued*:

- 1) the FDA approved the device as safe and effective for newly diagnosed GBM;
- 2) Published studies demonstrated the conclusive safety and effectiveness of TTFT;
- 3) The consensus of experts is that TTFT is safe and effective;
- 4) NCCN guidelines gave TTFT a higher level recommendation;
- 5) The most recent clinical trial of TTFT for GBM was halted because it would have been unethical to deny TTFT to the study participants that were not selected for treatment;
- 6) TTFT became widely adopted by the provider and payor communities; and
- 7) TTFT became the standard of care for newly diagnosed GBM.

Of course, Mr. Christenson also presented evidence of his own medical condition. Mr. Christenson had a life expectancy of six months, but has exceeded that by more than three years and has not shown any signs of progression.

In his decision, the ALJ ignored the foregoing and simply stated he was bound by the LCD. Respectfully, the ALJ's reasoning in this regard reflects an error in both the evidence on which an ALJ's decision is to be based, and the ALJ's role in the process. As prescribed by 42 C.F.R. § 405.1000(d), an ALJ's decision is based on the "administrative record", i.e., the record in the specific case. Thus, the fact that the LCD has not yet been revised should be considered in view of the Medicare beneficiary's condition and the overwhelming evidence that TTFT met Medicare's coverage criteria before the dates of service.

In the present case, Mr. Christenson offered evidence that TTFT had conferred a specific benefit to him, and is, literally, a life-saving treatment for his deadly form of brain cancer. The ALJ conceded the medical benefit to Mr. Christenson. It is difficult to imagine more compelling facts that support Medicare coverage. The ALJ's refusal to consider that evidence was an error of law.

C. ALJ's Are Not Bound By LCDs

Under the rules applicable to Medicare, ALJs and the MAC are not bound by an LCD but must explain their decision if they decline to follow one. 42 C.F.R. § 405.1062. Thus, even in the face of a perfectly valid LCD excluding coverage, an ALJ or the MAC may decline to follow it and order coverage. In this case, of course, the LCD has become invalid through the revision that issued on July 18, 2019. In the present case, the ALJ's claim that he is bound to follow an LCD contradicts the regulation. This is an error of law.

D. The Invalid LCD L34823 Does Not Apply

On July 18, 2019, the DMACs revised LCD L34823. The revision of an LCD after an LCD challenge has been filed has the same effect as a judicial ruling the LCD was invalid. Accordingly, the ALJ's application of the invalid LCD was an error of law.

E. Coverage Should Be Ordered

Where there is no applicable statute, NCD, or LCD, whether durable medical equipment should be covered is guided by 42 C.F.R. § 414.202. Further, to be covered, the device must be medically reasonable and necessary for the particular beneficiary.

In the present case, there was no dispute that the Optune device qualifies as DME. The evidence in the record showed the following: 1) the device can withstand repeated use (indeed, that is how the treatment works); 2) not being consumable in nature and having no moving parts, the device has an expected life of at least three years; 3) the device is primarily and customarily used to serve a medical purpose (indeed, it has no other purpose); 4) the device is generally not useful in absence of illness or injury (indeed, no other use is known); and 5) the device is

appropriate for use in the home (indeed, it is wearable and can be used both indoors and outdoors). No evidence to the contrary was submitted. Accordingly, the Optune device qualifies as DME.

With regard to whether the device is medically reasonable and necessary for Mr. Christenson, the data from the clinical trial for newly diagnosed glioblastomas demonstrated such remarkable effectiveness that the study was terminated early to enable those not receiving treatment during the clinical trial to receive the treatment. The FDA approved the device as effective. TTFT is included in the NCCN guidelines. Thus, the experts agree that the peer-reviewed literature supports offering to those afflicted with a GBM.

TTFT satisfies the other coverage criteria – the consensus of experts and widespread adoption. The consensus of experts (reflected in the NCCN guidelines and adoption by all the major medical centers in the United States), and acceptance by the relevant medical community (again in view of the inclusion in practice guidelines, the device has been prescribed in every state by hundreds of clinicians and is covered by all major payers), strongly support Medicare coverage. Further, of course, all of this evidence demonstrates that the medical community considers TTFT safe and effective.

Off course, Mr. Christenson's treating physician prescribed the device to treat his GBM. Where, as here, the treating physician makes a determination, significant reliance should be placed on that determination or there must be a reasoned basis for failing to do so. See *Klementowski v. Secretary of HHS*, 801 F. Supp. 1022 (W.D.N.Y. 1992) citing *State of New York v. Sullivan*, 927 F.2d 57, 60 (2d Cir. 1991).¹ This is especially compelling where, as in the case herein, there is "no direct conflicting evidence." *Kuebler v. Secretary of U.S. Dept. of Health & Human Services*, 579 F. Supp. 1436 (D.C. N.Y. 1984). In fact, the Ninth Circuit has commented that the treating physician's opinion should not be rejected without clear and convincing evidence to do so. *Vista Hill Foundation, Inc. v. Heckler*, 767 F.2d 556 (9th Cir. 1985). There is no "reasoned basis" for refusing to accept the opinion of Mr. Christenson's treating physician. See *Heart 4 Heart, Inc. v. Sebelius*, 2014 WL 3028684 (C.D. Illinois July 3, 2014) at 8 - 9.

Accordingly, coverage of Mr. Christenson's TTFT device should be ordered.

IV. Conclusion

The Optune system was reasonable and medically necessary when it was provided to Mr. Christenson. The denial is contrary to the facts and law. The ALJ committed fundamental errors of law and fact when he denied a Medicare beneficiary coverage of a service which has extended his life. Based on the foregoing, the Council should reverse Judge Watson's decision and order coverage of the Optune system for Mr. Christenson consistent with the standard of care.

¹ See also *Roddy v. Astrue*, 705 F.3d 631, 636, 637 (7th Cir. 2013); *Senn v. Astrue*, 2013 WL 63257 (E.D. Wis.).

Please contact me if you have any questions regarding this appeal.

Yours very truly,

A handwritten signature in black ink, appearing to read "Debra Pistorino Parrish". The signature is fluid and cursive, with a large initial "D" and "P".

Debra Pistorino Parrish

Enclosures:

Attachment 1: Appointment of Representative

Attachment 2: September 12, 2019 ALJ Decision

cc: D. Christenson
Maximus
C2C Innovative Solutions, Inc.
Novocure, Inc.

REQUEST FOR REVIEW OF ADMINISTRATIVE LAW JUDGE (ALJ) MEDICARE DECISION / DISMISSAL

| | |
|---------------------------------------------------------------------|-------------------------------------------------------------------------|
| 1. APPELLANT (the party requesting review) DAVID CHRISTENSON | 2. ALJ APPEAL NUMBER (on the decision or dismissal) 1-8630709341 |
| 3. BENEFICIARY* DAVID CHRISTENSON | 4. HEALTH INSURANCE CLAIM NUMBER (HICN)* 7QR9QM0QP33 |

*If the request involves multiple claims or multiple beneficiaries, attach a list of beneficiaries, HICNs, and any other information to identify all claims being appealed.

| | |
|----------------------------------------------------------|--------------------------------------------|
| 5. PROVIDER, PRACTITIONER, OR SUPPLIER Novocure, Inc. | 6. SPECIFIC ITEM(S) OR SERVICE(S) E0766 |
|----------------------------------------------------------|--------------------------------------------|

7. Medicare claim type: ☐ Part A ☒ Part B ☐ Part C - Medicare Advantage
☐ Part D - Medicare Prescription Drug Plan ☐ Entitlement/enrollment for Part A or Part B

8. Does this request involve authorization for an item or service that has not yet been furnished?

☐ Yes If Yes, skip to Block 9.

☒ No If No, Specific Dates of Service: 11/3/2018; 12/3/2018; 1/3/2019


9. If the request involves authorization for a prescription drug under Medicare Part D, would application of the standard appellate timeframe seriously jeopardize the beneficiary's life, health, or ability to regain maximum function (as documented by a physician) such that expedited review is appropriate? ☐ Yes ☒ No

I request that the Medicare Appeals Council review the ALJ's ☒ decision or ☐ dismissal order [check one] dated 9/12/2019. I disagree with the ALJ's action because (specify the parts of the ALJ's decision or dismissal you disagree with and why you think the ALJ was wrong):

Please see attached.

(Attach additional sheets if you need more space)

PLEASE ATTACH A COPY OF THE ALJ DECISION OR DISMISSAL ORDER YOU ARE APPEALING.

| | | | | | |
|-----------------------------------------------------|------------|--------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|------------------------|
| DATE | | | DATE 9/18/2019 | | |
| APPELLANT'S SIGNATURE (the party requesting review) | | | REPRESENTATIVE'S SIGNATURE (include signed appointment of representative if not already submitted.)  | | |
| PRINT NAME | | | PRINT NAME Debra M. Parrish | | |
| ADDRESS | | | ADDRESS 788 Washington Road | | |
| CITY, STATE, ZIP CODE | | | CITY, STATE, ZIP CODE Pittsburgh, PA 15228 | | |
| TELEPHONE NUMBER | FAX NUMBER | E-MAIL | TELEPHONE NUMBER | FAX NUMBER | E-MAIL |
| | | | 412-561-6250 | 412-561-6253 | debbie@dparrishlaw.com |

(SEE FURTHER INSTRUCTIONS ON PAGE 2)

If you have additional evidence, submit it with this request for review. If you need more time, you must request an extension of time in writing now, explaining why you are unable to submit the evidence or legal argument now.

If you are a provider, supplier, or a beneficiary represented by a provider or supplier, and your case was reconsidered by a Qualified Independent Contractor (QIC), the Medicare Appeals Council will not consider new evidence related to issues the QIC has already considered unless you show that you have a good reason for submitting it for the first time to the Medicare Appeals Council.

IMPORTANT: Include the HICN and ALJ Appeal Number on any letter or other material you submit.

This request must be received within 60 calendar days after you receive the ALJ's decision or dismissal, unless we extend the time limit for good cause. We assume you received the decision or dismissal 5 calendar days after it was issued, unless you show you received it later. If this request will not be received within 65 calendar days from the date on the decision or dismissal order, please explain why on a separate sheet.

You must file your request for review in writing with the Medicare Appeals Council at:

Department of Health and Human Services
 Departmental Appeals Board
 Medicare Appeals Council, MS 6127
 Cohen Building Room G-644
 330 Independence Ave., S.W.
 Washington, D.C. 20201

You may send the request for review by U.S. Mail, a common carrier such as FedEx, or by fax to (202) 565-0227. If you send a fax, please do not also mail a copy. **You must send a copy of your appeal to the other parties and indicate that all parties, to include all beneficiaries, have been copied on the request for review. For claims involving multiple beneficiaries, you may submit a copy of the cover letters issued or a spreadsheet of the beneficiaries and addresses who received a copy of the request for review.**

If you have any questions about your request for review or wish to request expedited review of a claim involving authorization of your prescription drug under Medicare Part D, you may call the Medicare Appeals Council's staff in the Medicare Operations Division of the Departmental Appeals Board at (202) 565-0100. You may also visit our web site at www.hhs.gov/dab for additional information on how to file your request for review.

PRIVACY ACT STATEMENT

The collection of information on this form is authorized by the Social Security Act (section 205(a) of title II, section 702 of title VII, section 1155 of Title XI, and sections 1852(g)(5), 1869(b)(1), 1871, 1872, and 1876(c)(5)(B) of title XVIII, as appropriate). The information provided will be used to further document your claim. Information requested on this form is voluntary, but failure to provide all or any part of the requested information may affect the determination of your claim. Information you furnish on this form may be disclosed by the Department of Health and Human Services or the Social Security Administration to another person or governmental agency only with respect to programs under the Social Security Act and to comply with Federal laws requiring the disclosure of information or the exchange of information between the Department of Health and Human Services, the Social Security Administration, or other agencies.

APPOINTMENT OF REPRESENTATIVE

| | |
|-------------------------------------|-----------------------------------------------------------------|
| NAME OF PARTY: David Christenson | MEDICARE OR NATIONAL PROVIDER IDENTIFIER NUMBER: 7QR9QM0QP33 |
|-------------------------------------|-----------------------------------------------------------------|

SECTION I: APPOINTMENT OF REPRESENTATIVE

To be completed by the party seeking representation (i.e., the Medicare beneficiary, the provider or the supplier):

I appoint this individual: Debra M. Parrish to act as my representative in connection with my claim or asserted right under Title XVIII of the Social Security Act (the "Act") and related provisions of Title XI of the Act. I authorize this individual to make any request; to present or to elicit evidence; to obtain appeals information; and to receive any notice in connection with my appeal, wholly in my stead. I understand that personal medical information related to my appeal may be disclosed to the representative indicated below.

| | | |
|------------------------------------------------------------------------|--------------|--------------------------------------------------|
| SIGNATURE OF PARTY SEEKING REPRESENTATION: <u>David Christenson</u> | | DATE: 1/26/2019 |
| STREET ADDRESS: 5754 Clevedon Lane | | PHONE NUMBER (with Area Code): (920) 203-5636 |
| CITY: Oshkosh | STATE: WI | ZIP: 54904 |

SECTION II: ACCEPTANCE OF APPOINTMENT

To be completed by the representative:

I, Debra M. Parrish, hereby accept the above appointment. I certify that I have not been disqualified, suspended, or prohibited from practice before the Department of Health and Human Services; that I am not, as a current or former employee of the United States, disqualified from acting as the party's representative; and that I recognize that any fee may be subject to review and approval by the Secretary.

I am a / an ATTORNEY (Debra M. Parrish)

(PROFESSIONAL STATUS OR RELATIONSHIP TO THE PARTY, E.G. ATTORNEY, RELATIVE, ETC.)

| | | |
|----------------------------------------------------|--------------|--------------------------------------------------|
| SIGNATURE OF REPRESENTATIVE: <u>[Signature]</u> | | DATE: 2-5-19 |
| STREET ADDRESS: 788 Washington Road | | PHONE NUMBER (with Area Code): (412) 561-6250 |
| CITY: Pittsburgh | STATE: PA | ZIP: 15228 |

SECTION III: WAIVER OF FEE FOR REPRESENTATION

Instructions: This section must be completed if the representative is required to, or chooses to waive their fee for representation. (Note that providers or suppliers that are representing a beneficiary and furnished the items or services may not charge a fee for representation and must complete this section.)

I waive my right to charge and collect a fee for representing _____ before the Secretary of the Department of Health and Human Services.

| | |
|---------------------|----------------|
| SIGNATURE: _____ | DATE: _____ |
|---------------------|----------------|

SECTION IV: WAIVER OF PAYMENT FOR ITEMS OR SERVICES AT ISSUE

Instructions: Providers or suppliers serving as a representative for a beneficiary to whom they provided items or services must complete this section if the appeal involves a question of liability under section 1879(a)(2) of the Act. (Section 1879(a)(2) generally addresses whether a provider/supplier or beneficiary did not know, or could not reasonably be expected to know, that the items or services at issue would not be covered by Medicare.)

I waive my right to collect payment from the beneficiary for the items or services at issue in this appeal if a determination of liability under §1879(a)(2) of the Act is at issue.

| | |
|---------------------|----------------|
| SIGNATURE: _____ | DATE: _____ |
|---------------------|----------------|

RECEIVED SEP 14 2019



Department of Health and Human Services
Office of the Secretary

OFFICE OF MEDICARE HEARINGS AND APPEALS

Cleveland Field Office
200 Public Square, Suite 1300
Cleveland, OH 44114-2316
216-615-4000 (Main)
216-615-7546 (ALJ Watson Team)
216-615-6735 (Fax)
866-236-5089 (Toll Free)

Date: September 12, 2019

D. CHRISTENSON
5754 CLEVEDON LN
OSHKOSH, WI 54904-9729

NOTICE OF DECISION

Appellant: D. CHRISTENSON
OMHA Appeal Number: 1-8630709341

Enclosed is the decision for the above case. This decision is based on the administrative record, including any evidence or testimony presented at the hearing, if one was held. The decision is not precedential, does not release the appellant from civil or criminal liability, and may be reopened at any time if it was procured by fraud or similar fault. In addition, the decision may be reopened within 180 calendar days from the date of the decision for good cause. Good cause exists when there is new and material evidence that was not available or known at the time of the decision and may result in a different conclusion, or when the evidence that was considered clearly shows on its face that an obvious error was made at the time of the decision.

What if I disagree with the decision?

If you disagree with the decision, you may file an appeal with the Medicare Appeals Council. Other parties may also appeal the decision. In addition, the Medicare Appeals Council may decide to review the decision on its own motion. If no party appeals the decision and the Medicare Appeals Council does not review the decision, the decision is binding on all parties and you and the other parties will not have the right to ask a federal court to review the decision.

If you are not already represented, you may appoint an attorney or other person to represent you.

How much time do I have to file an appeal?

The Medicare Appeals Council must receive your written appeal **within 60 calendar days** of the date that you receive this notice. The Medicare Appeals Council assumes you received this notice 5 calendar days after the date of the notice unless you show that you did not receive it within the 5-day period.

The Medicare Appeals Council will dismiss a late request for review unless you show that you had a good reason for not filing it on time.

How do I file an appeal?

To appeal, you must ask the Medicare Appeals Council to review the decision. Your appeal must be in writing, except that a request for expedited review of a Part D decision may be made orally as described below. Your appeal must identify the parts of the decision that you disagree with, and explain why you disagree.

You may submit a written request for review to the Medicare Appeals Council using one of three available methods: mail, fax, or electronic filing (E-File). **Please do not submit your request for review using more than one method.** Regardless of how you file your appeal, **you must always send a copy of your written request for review to the other parties who received a copy of the decision.**

If you are filing a written request for review, you may use the enclosed *Request for Review* (form DAB-101), or you may write a letter containing the following:

- The beneficiary's/enrollee's name (and telephone number for Part D appeals);
- The beneficiary's/enrollee's Medicare number (Health Insurance Claim Number or Medicare Beneficiary Identifier);
- The item(s), service(s), or specific Part D drug(s) in dispute;
- The specific date(s) the item(s) or service(s) were provided, if applicable;
- For Part D appeals, the plan name;
- For Part D appeals, the OMHA Appeal Number on the adjudicator's decision;
- For Part D appeals requesting expedited review, a statement that you are requesting expedited review;
- The date of the adjudicator's decision (not required for Part D appeals); and
- Your name and signature, and, if applicable, the name and signature of your representative.

Filing by mail:

Mail your appeal and a copy of the enclosed decision to:

Department of Health and Human Services
Departmental Appeals Board
Medicare Appeals Council, MS 6127
Cohen Building Room G-644
330 Independence Ave., S.W.
Washington, D.C. 20201

Filing by fax:

Fax your appeal and a copy of the enclosed decision to (202) 565-0227.

Filing by computer:

Using your web browser, visit the Medicare Operations Division Electronic Filing System (MOD E-File) website at <https://dab.efile.hhs.gov/mod>.

To file a new appeal using MOD E-File, you will need to register by:

- (1) Clicking **Register** on the MOD E-File home page;
- (2) Entering the information requested on the “Register New Account” form; and
- (3) Clicking **Register Account** at the bottom of the form.

You will use the email address and password you provided during registration to access MOD E-File at <https://dab.efile.hhs.gov/mod/users/new>. You will be able to use MOD E-File to file and access the specific materials for appeals to which you are a party or a party’s representative. You may check the status of any appeal on the website homepage without registering.

Once registered, you may file your appeal by:

- (1) Logging into MOD E-File;
- (2) Clicking the **File New Appeal** menu button on the top right of the screen;
- (3) Selecting the type of appeal you are filing (Request for Review or Request for Escalation); and
- (4) Entering the requested Appeal Information and uploading the requested Appeal Documents on the “File New Appeal – Medicare Operations Division” form. You are required to provide information and documents marked with an asterisk.

At a minimum, the Medicare Appeals Council requires an appellant to file a signed Request for Review and a copy of the enclosed decision. All documents should be submitted in Portable Document Format (PDF) whenever possible. Any document, including a Request for Review, will be deemed to have been filed on a given day, if it is uploaded to MOD E-File on or before 11:59 p.m. EST of that day.

Currently, the documents that may be filed electronically are the:

- (1) Request for Review;
- (2) Appointment of Representative form (OMB Form 0938-0950);
- (3) Copy of Administrative Law Judge or attorney adjudicator decision;
- (4) Memorandum or brief or other written statement in support of your appeal; and
- (5) Request to Withdraw your appeal

No other documents aside from the five (5) listed categories above may be submitted through MOD E-File.

Filing by oral request (for expedited review only):

Oral requests for expedited review of a Part D decision may be made by telephone to (866) 365-8204. You must provide the information listed in the bullet points above and a statement that you are requesting an expedited review within 60 calendar days after receipt of this notice of

decision. The Medicare Appeals Council will document the oral request in writing and maintain the documentation in the case file.

Please note that your request for review will only be expedited if (1) the appeal involves an issue specified in 42 C.F.R. § 423.566(b), but does not include solely a request for payment of a Part D drug that has already been furnished, and (2) the prescribing physician (or other prescriber) indicates, or the Medicare Appeals Council determines, that the standard time frame may seriously jeopardize your life, health, or ability to regain maximum function.

How will the Medicare Appeals Council respond to my appeal?

The Medicare Appeals Council will limit its review to the issues raised in the appeal, unless the appeal is filed by an unrepresented beneficiary/enrollee. It may change the parts of the decision that you agree with. It may adopt, modify, or reverse the decision, in whole or in part, or it may send the case back to OMHA for further action. It may also dismiss your appeal.

Questions?

You may call or write our office. A toll-free phone number and mailing address are at the top of this notice.

Additional information about filing an appeal with the Medicare Appeals Council is available at <http://www.hhs.gov/dab/>. You can also call the Medicare Appeals Council's staff in the Medicare Operations Division of the Departmental Appeals Board at (202) 565-0100 or (866) 365-8204 (toll free), if you have questions about filing an appeal.

cc:

DEBRA M PARRISH
788 WASHINGTON RD
PITTSBURGH, PA 15228

C2C Innovative Solutions, Inc.
DME QIC Appeals—ALJ
P.O. Box 44006
Jacksonville, FL 32231-4006

NOVOCURE INC.
195 Commerce Way
Portsmouth, NH 03801

MAXIMUS
DME QIC Appeals—ALJ
3750 Monroe Avenue
Pittsford, NY 14534-1302

Enclosures:

OMHA-152, Decision
DAB-101, Request for Review

REQUEST FOR REVIEW OF ADMINISTRATIVE LAW JUDGE (ALJ) MEDICARE DECISION / DISMISSAL

1. APPELLANT (the party requesting review)

2. ALJ APPEAL NUMBER (on the decision or dismissal)

3. BENEFICIARY*

4. HEALTH INSURANCE CLAIM NUMBER (HICN)*

*If the request involves multiple claims or multiple beneficiaries, attach a list of beneficiaries, HICNs, or other information to identify all claims being appealed.

5. PROVIDER, PRACTITIONER, OR SUPPLIER

6. SPECIFIC ITEM(S) OR SERVICE(S)

7. Medicare claim type: ☐ Part A ☐ Part B ☐ Part C - Medicare Advantage
☐ Part D - Medicare Prescription Drug Plan ☐ Entitlement/enrollment for Part A or Part B

8. Does this request involve authorization for an item or service that has not yet been furnished?

☐ Yes If Yes, skip to Block 8.
☐ No If No, Specific Dates of Service:

9. If the request involves authorization for a prescription drug under Medicare Part D, would application of the standard appellate timeframe seriously jeopardize the beneficiary's life, health, or ability to regain maximum function (as documented by a physician) such that expedited review is appropriate? ☐ Yes ☐ No

I request that the Medicare Appeals Council review the ALJ's ☐ decision or ☐ dismissal order [check one] dated _____. I disagree with the ALJ's action because (specify the parts of the ALJ's decision or dismissal you disagree with and why you think the ALJ was wrong):

(Attach additional sheets if you need more space)

PLEASE ATTACH A COPY OF THE ALJ DECISION OR DISMISSAL ORDER YOU ARE APPEALING.

| | | | | | |
|-----------------------------------------------------|------------|--------|-----------------------------------------------------------------------------------|------------|--------|
| DATE | | | DATE | | |
| APPELLANT'S SIGNATURE (the party requesting review) | | | REPRESENTATIVE'S SIGNATURE (include signed appointment if not already submitted.) | | |
| PRINT NAME | | | PRINT NAME | | |
| ADDRESS | | | ADDRESS | | |
| CITY, STATE, ZIP CODE | | | CITY, STATE, ZIP CODE | | |
| TELEPHONE NUMBER | FAX NUMBER | E-MAIL | TELEPHONE NUMBER | FAX NUMBER | E-MAIL |

(SEE FURTHER INSTRUCTIONS ON PAGE 2)

If you have additional evidence, submit it with this request for review. If you need more time, you must request an extension of time in writing now, explaining why you are unable to submit the evidence or legal argument now.

If you are a provider, supplier, or a beneficiary represented by a provider or supplier, and your case was reconsidered by a Qualified Independent Contractor (QIC), the Medicare Appeals Council will not consider new evidence related to issues the QIC has already considered unless you show that you have a good reason for submitting it for the first time to the Medicare Appeals Council.

IMPORTANT: Include the HICN and ALJ Appeal Number on any letter or other material you submit.

This request must be received within 60 calendar days after you receive the ALJ's decision or dismissal, unless we extend the time limit for good cause. We assume you received the decision or dismissal 5 calendar days after it was issued, unless you show you received it later. If this request will not be received within 65 calendar days from the date on the decision or dismissal order, please explain why on a separate sheet.

You must file your request for review in writing with the Medicare Appeals Council at:

Department of Health and Human Services
Departmental Appeals Board
Medicare Appeals Council, MS 6127
Cohen Building Room G-644
330 Independence Ave., S.W.
Washington, D.C. 20201

You may send the request for review by U.S. Mail, a common carrier such as FedEx, or by fax to (202) 565-0227. If you send a fax, please do not also mail a copy. **You must send a copy of your appeal to the other parties and indicate that all parties, to include all beneficiaries, have been copied on the request for review. For claims involving multiple beneficiaries, you may submit a copy of the cover letters issued or a spreadsheet of the beneficiaries and addresses who received a copy of the request for review.**

If you have any questions about your request for review or wish to request expedited review of a claim involving authorization of your prescription drug under Medicare Part D, you may call the Medicare Appeals Council's staff in the Medicare Operations Division of the Departmental Appeals Board at (202) 565-0100. You may also visit our web site at www.hhs.gov/dab for additional information on how to file your request for review.

PRIVACY ACT STATEMENT

The collection of information on this form is authorized by the Social Security Act (section 205(a) of title II, section 702 of title VII, section 1155 of Title XI, and sections 1852(g)(5), 1869(b)(1), 1871, 1872, and 1876(c)(5)(B) of title XVIII, as appropriate). The information provided will be used to further document your claim. Information requested on this form is voluntary, but failure to provide all or any part of the requested information may affect the determination of your claim. Information you furnish on this form may be disclosed by the Department of Health and Human Services or the Social Security Administration to another person or governmental agency only with respect to programs under the Social Security Act and to comply with Federal laws requiring the disclosure of information or the exchange of information between the Department of Health and Human Services, the Social Security Administration, or other agencies.



Department of Health and Human Services
OFFICE OF MEDICARE HEARINGS AND APPEALS
Cleveland, Ohio

| | |
|------------------------------------|------------------------------------------------------------|
| Appeal of: D. CHRISTENSON | OMHA Appeal No.: 1-8630709341 |
| Beneficiary: D. CHRISTENSON | Medicare: Part B |
| Medicare No.: *3639A | Before: Scott M. Watson Administrative Law Judge |

DECISION

After carefully considering the evidence, arguments and testimony presented in the record, an **UNFAVORABLE** decision is entered against the Appellant/Beneficiary, D. Christenson.

Procedural History

The Appellant requested coverage under Medicare Part B of a tumor treatment field therapy (TTFT) device called Optune which was supplied by Novocure, Inc. (Provider) on November 13, 2018, December 3, 2018, and January 3, 2019. A claim for the device was submitted to a Medicare Administrative Contractor (MAC), which was denied initially and upon redetermination. On June 7, 2019, a Qualified Independent Contractor (QIC), C2C Solutions, Inc., issued an unfavorable reconsideration decision.

The Appellant timely filed a request for an Administrative Law Judge (ALJ) hearing. The amount in controversy meets the jurisdictional requirements for a hearing. See 42 C.F.R. §§ 405.1006 and 422.5600(b).

An administrative hearing was held by telephone on August 28, 2019. The Appellant was represented by Attorney Debra Parrish. Timothy Parks, RN, of Novocure also testified on behalf of the Appellant. The relevant CMS contractors were sent notice of the hearing but declined to participate.

All exhibits were admitted into evidence without objection.

Issue

The issue is whether Medicare Part B covers the TTFT device to assist with the treatment/management of the Appellant's recurrent glioblastoma.

Findings of Fact

The following facts are established by the preponderance of the evidence.

1. The Appellant, a 65-year old man, was diagnosed with glioblastoma (“GBM”) in July 2015. He then underwent successful resection, chemotherapy, and radiation therapy to treat his GBM. But in early 2016, post-treatment studies showed a size increase in the GBM. The Appellant’s physician ordered one year of TTFT in combination with temozolomide to treat the recurrent GBM. In February 2017, the Appellant began receiving only TTFT for his recurrent GBM. (Park’s testimony; *See* also Appellant’s pre-hearing brief)
2. On September 19, 2018, the Appellant underwent an MRI of the brain. The image showed that the tumor was stable. (Exh. 2, p. 20).
3. The appeal file includes a “Proposed Local Coverage Determination (LCD): Tumor Treatment Field Therapy (TTFT) (DL34823)” that states that “tumor treatment field therapy (E0766) will be denied as not reasonable and necessary for the treatment of *recurrent* GBM.” (Exh. 5, p. 20).
4. The revised LCD L34823, with an effective date of September 1, 2019, expressly states that TTFT will be denied as not reasonable and necessary for treatment of *recurrent* GBM. The LCD also provides that the DME-MACs received a request to reconsider the decision on recurrent GBM in 2018; however, the requestor, Novocure, did not submit new evidence in support of the revised coverage for recurrent disease. The DME-MACs therefore concluded that the request was invalid.¹

Legal Framework

I. ALJ Review Authority

A. Jurisdiction

An individual who, or an organization that, is dissatisfied with the reconsideration of an adverse organization determination is entitled to a hearing before the Secretary of the Department of Health and Human Services (HHS), provided there is a sufficient amount in controversy and a request for hearing is filed in a timely manner. Social Security Act (Act) § 1859(g)(5); see 42 C.F.R. § 422.600. The request for hearing is timely filed if filed within 60 days of the date of notice of a reconsidered determination. 42 C.F.R. § 422.602.

In implementing this statutory directive, the Secretary delegated authority to administer the nationwide hearings and appeals system for the Medicare program to the Office of Medicare Hearings and Appeals (OMHA). See 70 Fed. Reg. 36386, 36387 (June 23, 2005). ALJs within

¹ *See*

<https://med.noridianmedicare.com/documents/2230703/7218263/Tumor+Treatment+Field+Therapy+%28TTFT%29%20LCD+and+PA/8f195ce1-c8e1-4c92-8578-f2b8996e4507>

OMHA issue the final decisions of the Secretary, except for decisions reviewed by the Medicare Appeals Council.

B. Scope of Review

Medicare Advantage Organization determinations and appeals are governed by the regulations in 42 C.F.R. §§ 422.560 through 422.626. Unless otherwise noted, the ALJ hearing procedures set forth in 42 C.F.R. §§ 405.1000 through 405.1064 apply to Medicare Advantage appeals, to the extent they are appropriate. 42 C.F.R. § 422.562(d).

The issues before the ALJ include all the issues brought out in the initial determination, redetermination, or reconsideration that were not decided entirely in the Appellant's favor. 42 C.F.R. § 405.1032(a). However, if evidence presented before the hearing causes the ALJ to question a favorable portion of the determination, he or she may notify the parties before the hearing and may consider it an issue at the hearing. *Id.*

C. Standard of Review

The OMHA is staffed with ALJs who conduct de novo hearings. 42 C.F.R. § 405.1000(d). A de novo review means the ALJ reviews the evidence without regard to the findings in the prior determinations on the claim and makes an independent assessment based on the evidence and the controlling laws. However, the burden of proving each element of a Medicare claim lies with the appellant and is satisfied by submitting sufficient evidence in accordance with Medicare rules. See e.g., Act §§ 1814(a)(1), 1815(b), and 1833(e); see also 42 C.F.R. §§ 424.5(a)(6), 405.1018, 405.1028, and 405.1030.

II. Principles of Law

A. Statutes and Regulations

Eligibility for Medicare benefits is determined under Title XVIII of the Act, 42 U.S.C. § 1801 et seq., and federal regulations set forth in Title 42 of the Code of Federal Regulations.

According to section 1862(a)(1)(A) of the Act, no payment may be made under Original Medicare for any expenses incurred for items or services that are "not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." See 42 U.S.C. § 1395y(a)(1)(A); see also 42 C.F.R. § 41.115(k)(1).

B. Policy and Guidance

Section 1871(a)(2) of the Act provides that no rule, requirement or statement of policy, other than a national coverage determination (NCD), can establish or change a substantive legal standard governing the scope of the benefits or payment for services under the Medicare program unless promulgated as a regulation by CMS. NCDs promulgated by the Secretary of HHS under the authority of Section 1862(a)(1) of the Act dictate the criteria under which Medicare covers specified services, procedures or supplies. NCDs are binding upon ALJs. 42 C.F.R. § 405.1060(a)(4); see 42 C.F.R. § 405.1060(b)(1) ("An ALJ may not disregard, set aside or otherwise review an NCD").

Although not subject to the force and effect of law, CMS and its contractors issue policies, manuals and guidelines that describe criteria for coverage of selected types of medical items and services in the form of manuals and local coverage determinations (LCDs). 42 C.F.R. § 405.1062 states that an ALJ is not bound by LCDs or CMS program guidance, such as program memoranda and manual instructions, but will give substantial deference to these policies if they are applicable to a particular case. If an ALJ declines to follow a policy in a particular case, the ALJ decision must explain the reasons why the policy was not followed. An ALJ decision to disregard such policy applies only to the specific claim being considered and does not have precedential effect.

The DME MAC with jurisdiction over this appeal applied LCD L34823 (Tumor Treatment Field Therapy (TTFT)). The applicable LCD provides that TTFT (E0766) will be denied as not reasonable and necessary.

Analysis

The Appellant seeks reimbursement for TTFT (E0766) to treat recurrent GBM. The QIC and the MAC denied the request because a Medicare local coverage determination states “[t]umor treatment field therapy (E0766) will be denied as not reasonable and necessary.” (LCD L34823). For the reasons set forth below, I agree with the previous denial and conclude that Medicare Part B does not provide for coverage of TTFT for the treatment of the Appellant’s recurrent GBM.

CMS has determined that the TTFT Optune device (E0766) meets the definition of durable medical equipment (DME). (See Policy Article A52711). Medicare covers DME when sufficient information is provided to conclude that the DME was medically reasonable and necessary for the treatment or management of an illness or medical condition. See Act § 1862(a)(1)(A). Generally, CMS and its contractors publish coverage policies and guidance to apply when considering whether or not certain DME is reasonable and necessary. See Act § 1869(f)(2)(B); 42 C.F.R. § 405.1060; *MPIM*, ch 13, § 13.5.1

In this case, the MAC and the QIC relied on LCD L34823 to support denial of the Appellant’s request for coverage. The pertinent LCD provides conclusory language stating “[t]umor treatment field therapy (E0766) will be denied as not reasonable and necessary.” The LCD does not elaborate further as to why TTFT is deemed not reasonable and necessary.

Since the publication of this LCD, the DME-MACs, through their medical directors, have conceded that LCD L34823 only precludes coverage of TTFT for **recurrent** GBM as not reasonable and necessary. The DME-MACs have explicitly stated that LCD L324823 does not address coverage for **newly diagnosed** GBM. However, the issue in this case pertains to coverage of TTFT for **recurrent** GBM, which is addressed by L34823. I therefore find that L34823 should be applied to find that TTFT for the treatment of recurrent GBM is considered not reasonable and necessary.

While I understand that this treatment has been effective for the Appellant since he began receiving the treatment, I am bound to follow Medicare rules and regulations. I find that there is not sufficient evidence to show that L34823 does not apply to the Beneficiary’s diagnosis, nor is

there sufficient evidence to show that the LCD should be disregarded. Neither the old nor the revised LCD provides for coverage of TTFT for the treatment of recurrent GBM. Therefore, based upon the record, I find that the Appellant is not entitled to coverage of the Optune tumor treatment field therapy (E0766) received on November 13, 2018, December 3, 2018, and January 3, 2019.

Where the Medicare coverage requirements have not been met, waiver of liability pursuant to section 1879(a) of the Social Security Act, 42 U.S.C. § 1395pp(a), might apply. A provider will be held liable for the cost of services unless it did not know, and reasonably could not have known, that the services would not be covered. The same statutory provision applies to beneficiaries, although the “reasonably could not have known” standard is interpreted and applied differently in their case due to their presumed unfamiliarity with the numerous publications that govern Medicare coverage.

There was no Advance Beneficiary Notice (“ABN”) included in the file. The Beneficiary neither knew, nor reasonably should have been expected to know, that services would not be covered by Medicare. Novocure (“Provider”) is presumed to have knowledge of published Medicare coverage rules, regulations, and guidelines. The Provider either knew, or reasonably should have been expected to know, that the services denied would not be covered by Medicare. As a result, the Provider is not eligible for a waiver of liability, pursuant to § 1879 of the Act, 42 U.S.C. § 1395pp(a), and is liable for the non-covered charges.

Conclusions of Law

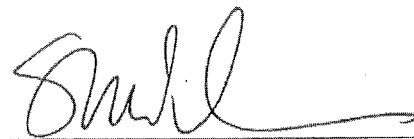
Medicare Part B does not cover the tumor treatment field therapy (E0766) for recurrent GBM; therefore, the Appellant is not entitled to coverage of the TTFT (E0776) provided to the Appellant on November 13, 2018, December 3, 2018, and January 3, 2019.

Novocure remains financially liable for the denied charges.

Order

The Medicare contractor is **DIRECTED** to process the claim in accordance with this decision.

SO ORDERED



Scott M. Watson
Administrative Law Judge

Dated: **SEP 12 2019**



Department of Health and Human Services
OFFICE OF MEDICARE HEARINGS AND APPEALS
Cleveland, Ohio

| | |
|------------------------------------|----------------------------------------------------------------|
| Appeal of: D. CHRISTENSON | OMHA Appeal No.: 1-8630709341 |
| Beneficiary: D. CHRISTENSON | Medicare: Part B |
| Medicare No.: *****3639A | Before: Scott Watson Administrative Law Judge |

EXHIBIT LIST

| EXHIBIT NUMBER | DESCRIPTION | PAGE NUMBERS |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------|-----------------|
| 1 | Initial, Redetermination and Reconsideration Procedural Documents, Articles and literature, Redacted ALJ decisions | 1-3145 |
| 2 | Medical Records/Evidence Received by CMS Contractors | 1-23 |
| 3 | Request for ALJ Hearing / Appointment of representative form (Beneficiary) 6/17/19 Request for ALJ hearing (Novocure) 7/1/19 | 1-12 |
| 4 | OMHA Proceedings Notice of hearing 7/1/19 Response to NOH 7/5/19 | 1-10 |
| 5 | Pre-Hearing Brief (Beneficiary Rep) 7/8/19 | 1-47 |

Dated: August 12, 2019

¹ Some materials in the exhibited record are dual sided. References to the second side include a notation of (reverse). For example, "Ex. 1, p. 1 (reverse)." The second side of a dual sided page is not included in the page count for the page number range.



Departmental Appeals Board, MS 6127
Medicare Appeals Council
330 Independence Avenue
Cohen Building, Room G-644
Washington, DC 20201
(202)565-0100/Toll Free:1-866-365-8204

Date: **JAN 22 2020**

ALJ Appeal Numbers: 1-7884275431 & 16 others
Docket Numbers: M-19-1261 & 30 others

ACKNOWLEDGMENT OF ESCALATION REQUESTS
AND NOTICE OF STAY

Parrish Law Offices
Debra Parrish
788 Washington Rd.
Pittsburgh, PA 15228

Dear Ms. Parrish:

The Medicare Appeals Council (Council) has received your requests to escalate the appeals listed in Attachment A to Federal district court. The Council previously received your requests for review for these appeals. The 90-day time frame for the Council to issue a decision, dismissal, or remand order has expired. *See* 42 C.F.R. § 405.1100(c). Due to the large number of pending appeals, the Council is unable to issue a decision, dismissal, or remand order within five calendar days of your request to escalate to Federal district court. 42 C.F.R. § 405.1132(a)(1). Under these circumstances, the regulations permit you to bypass Council review and seek review of the ALJ's decisions in Federal district court. 42 C.F.R. § 405.1132(a)(2).

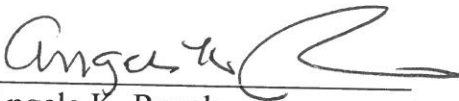
In order to escalate, you must file an action in Federal district court within 60 calendar days after you receive this notice and the amount in controversy must be \$1,670 or more. 42 C.F.R. §§ 405.1132(b), 405.1136(a)(1); *see also* 84 Fed. Reg. 53,445 (Oct. 7, 2019). If you cannot file your complaint within 60 days, you may ask the Council to extend the time in which you may begin a civil action. However, the Council will only extend the time if you provide a good reason for not meeting the deadline. Your reason must be set forth clearly in your request. 42 C.F.R. § 405.1134. If you do not file an action in Federal district court, then your appeals will remain before the Council. 42 C.F.R. § 405.1136(a)(2).

If a civil action is commenced, the complaint should name the Secretary of Health and Human Services as the defendant and should include the Council docket numbers and ALJ appeal numbers that you are appealing. 42 C.F.R.

§ 405.1136(d). The Secretary must be served by sending a copy of the summons and complaint by registered or certified mail to the General Counsel, Department of Health and Human Services, 200 Independence Avenue, S.W., Washington, D.C. 20201. In addition, you must serve the United States Attorney for the district in which you file your complaint and the Attorney General of the United States. *See* rules 4(c) and (i) of the Federal Rules of Civil Procedure and 45 C.F.R. § 4.1.

Additionally, the supplier filed a separate request for review in each of the appeals for which you seek escalation. *See* Attachment B. This letter serves as notice to all parties that the Council will stay the supplier's requests for review until the Federal district court issues a final determination on the escalated appeals or the time period for filing a complaint in district court expires.

Sincerely,


Angela K. Roach
Administrative Appeals Judge

cc: Novocure
Beneficiaries

Attachment A

Appeals Escalated to Federal district court

| Docket Number | ALJ Appeal Number(s) |
|---------------|-----------------------------|
| M-19-1261 | 1-7884275431 |
| M-19-2164 | 1-8411344383 |
| M-19-2173 | 1-8136495060 |
| M-19-2218 | 1-8411055191 & 1-8411055450 |
| M-19-2233 | 1-8390277469 |
| M-19-2426 | 3-8503660334 |
| M-19-2499 | 1-8429561876 |
| M-19-2560 | 1-8454636221 |
| M-19-2648 | 1-8510955262 |
| M-19-2649 | 3-8472551932 |
| M-19-2719 | 1-8393258352 |
| M-19-2723 | 1-8411066311 |
| M-19-2777 | 1-8630709341 |
| M-19-2780 | 1-8415607840 |
| M-19-2836 | 1-8665714599 |

Attachment B
Stayed Supplier Appeals

| Docket Number | ALJ Appeal Number |
|------------------------|-----------------------------|
| M-19-1380 | 1-7884275431 |
| M-19-2169 | 1-8411344383 |
| M-19-2179 | 1-8136495060 |
| M-19-2227 | 1-8411055191 & 1-8411055450 |
| M-19-2237 | 1-8390277469 |
| M-19-2275 ¹ | 1-8071086400 |
| M-19-2543 | 3-8503660334 |
| M-19-2542 | 1-8429561876 |
| M-19-2565 | 1-8454636221 |
| M-19-2750 | 1-8510955262 |
| M-19-2751 | 3-8472551932 |
| M-19-2810 | 1-8393258352 |
| M-20-75 | 1-8411066311 |
| M-19-2981 | 1-8630709341 |
| M-19-2985 | 1-8415607840 |
| M-19-2990 | 1-8665714599 |

¹ The beneficiary appeal associated with docket number M-19-2275 is docketed as M-19-2250. The Council previously acknowledged the beneficiary's request to escalate her appeal in a separate action.



September 26, 2019

Department of Health and Human Services
Departmental Appeals Board
Medicare Appeals Council, MS 6127
Cohen Building, Room G-644
330 Independence Ave., S.W.
Washington, D.C. 20201

Re: ALJ Appeal No.: 1-8630709341
Decision Date: 9/12/2019
Appellant: Novocure
Beneficiary: David Christenson
HICN: #####QRP33
Dates of Service: 11/3/2018, 12/3/2018, 1/3/2019
Service: E0766

Dear Medicare Appeals Council:

Novocure appeals the above-captioned ALJ decision on the issues and for the reasons articulated in the beneficiary appeal filed on 9/18/2019 and adopts them and incorporates them as if fully restated herein.

Timothy B Parks
Clinical Appeals Specialist

Direct:: 603 570 9398
Fax: 603-718-3294
Email: tparks@novocure.com
195 Commerce Way
Portsmouth, NH 03801
United States

cc: Debra M. Parrish for David Christenson

REQUEST FOR REVIEW OF ADMINISTRATIVE LAW JUDGE (ALJ) MEDICARE DECISION / DISMISSAL

| | |
|---------------------------------------------------------------|---------------------------------------------------------------------|
| 1. APPELLANT (the party requesting review) Novocure | 2. ALJ APPEAL NUMBER (on the decision or dismissal) 1-8630709341 |
| 3. BENEFICIARY* David Christenson | 4. HEALTH INSURANCE CLAIM NUMBER (HICN)* 7QR9QM0QP33 |

*If the request involves multiple claims or multiple beneficiaries, attach a list of beneficiaries, HICNs, and any other information to identify all claims being appealed.

| | |
|-----------------------------------------------------------|--------------------------------------------|
| 5. PROVIDER, PRACTITIONER, OR SUPPLIER Novocure | 6. SPECIFIC ITEM(S) OR SERVICE(S) E0766 |
|-----------------------------------------------------------|--------------------------------------------|

7. Medicare claim type: ☐ Part A ☒ Part B ☐ Part C - Medicare Advantage
☐ Part D - Medicare Prescription Drug Plan ☐ Entitlement/enrollment for Part A or Part B

8. Does this request involve authorization for an item or service that has not yet been furnished?

☐ Yes If Yes, skip to Block 9.

☒ No If No, Specific Dates of Service: 11/3/2018, 12/3/2018, 1/3/2019


9. If the request involves authorization for a prescription drug under Medicare Part D, would application of the standard appellate timeframe seriously jeopardize the beneficiary's life, health, or ability to regain maximum function (as documented by a physician) such that expedited review is appropriate? ☐ Yes ☒ No

I request that the Medicare Appeals Council review the ALJ's ☒ decision or ☐ dismissal order [check one] dated 9/12/2019. I disagree with the ALJ's action because (specify the parts of the ALJ's decision or dismissal you disagree with and why you think the ALJ was wrong):

Novocure appeals the ALJ decision on the issues and reasons articulated in the beneficiary appeal filed on 9/18/2019

(Attach additional sheets if you need more space)

PLEASE ATTACH A COPY OF THE ALJ DECISION OR DISMISSAL ORDER YOU ARE APPEALING.

| | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|-----------------------------------------------------------------------------------------------------|--|
| DATE 9/26/2019 | | DATE | |
| APPELLANT'S SIGNATURE (the party requesting review)  | | REPRESENTATIVE'S SIGNATURE (include signed appointment of representative if not already submitted.) | |
| PRINT NAME Timothy B Parks | | PRINT NAME | |
| ADDRESS 195 Commerce Way | | ADDRESS | |
| CITY, STATE, ZIP CODE Portsmouth, NH | | CITY, STATE, ZIP CODE | |
| TELEPHONE NUMBER (603) 570-9398 | FAX NUMBER (603) 718-3294 | E-MAIL TParks@Novocure.com | |

(SEE FURTHER INSTRUCTIONS ON PAGE 2)

If you have additional evidence, submit it with this request for review. If you need more time, you must request an extension of time in writing now, explaining why you are unable to submit the evidence or legal argument now.

If you are a provider, supplier, or a beneficiary represented by a provider or supplier, and your case was reconsidered by a Qualified Independent Contractor (QIC), the Medicare Appeals Council will not consider new evidence related to issues the QIC has already considered unless you show that you have a good reason for submitting it for the first time to the Medicare Appeals Council.

IMPORTANT: Include the HICN and ALJ Appeal Number on any letter or other material you submit.

This request must be received within 60 calendar days after you receive the ALJ's decision or dismissal, unless we extend the time limit for good cause. We assume you received the decision or dismissal 5 calendar days after it was issued, unless you show you received it later. If this request will not be received within 65 calendar days from the date on the decision or dismissal order, please explain why on a separate sheet.

You must file your request for review in writing with the Medicare Appeals Council at:

Department of Health and Human Services
Departmental Appeals Board
Medicare Appeals Council, MS 6127
Cohen Building Room G-644
330 Independence Ave., S.W.
Washington, D.C. 20201

You may send the request for review by U.S. Mail, a common carrier such as FedEx, or by fax to (202) 565-0227. If you send a fax, please do not also mail a copy. **You must send a copy of your appeal to the other parties and indicate that all parties, to include all beneficiaries, have been copied on the request for review. For claims involving multiple beneficiaries, you may submit a copy of the cover letters issued or a spreadsheet of the beneficiaries and addresses who received a copy of the request for review.**

If you have any questions about your request for review or wish to request expedited review of a claim involving authorization of your prescription drug under Medicare Part D, you may call the Medicare Appeals Council's staff in the Medicare Operations Division of the Departmental Appeals Board at (202) 565-0100. You may also visit our web site at www.hhs.gov/dab for additional information on how to file your request for review.

PRIVACY ACT STATEMENT

The collection of information on this form is authorized by the Social Security Act (section 205(a) of title II, section 702 of title VII, section 1155 of Title XI, and sections 1852(g)(5), 1869(b)(1), 1871, 1872, and 1876(c)(5)(B) of title XVIII, as appropriate). The information provided will be used to further document your claim. Information requested on this form is voluntary, but failure to provide all or any part of the requested information may affect the determination of your claim. Information you furnish on this form may be disclosed by the Department of Health and Human Services or the Social Security Administration to another person or governmental agency only with respect to programs under the Social Security Act and to comply with Federal laws requiring the disclosure of information or the exchange of information between the Department of Health and Human Services, the Social Security Administration, or other agencies.

RECEIVED SEP 14 2019



Department of Health and Human Services
Office of the Secretary

OFFICE OF MEDICARE HEARINGS AND APPEALS

Cleveland Field Office
200 Public Square, Suite 1300
Cleveland, OH 44114-2316
216-615-4000 (Main)
216-615-7546 (ALJ Watson Team)
216-615-6735 (Fax)
866-236-5089 (Toll Free)

Date: September 12, 2019

D. CHRISTENSON
5754 CLEVEDON LN
OSHKOSH, WI 54904-9729

NOTICE OF DECISION

Appellant: D. CHRISTENSON
OMHA Appeal Number: 1-8630709341

Enclosed is the decision for the above case. This decision is based on the administrative record, including any evidence or testimony presented at the hearing, if one was held. The decision is not precedential, does not release the appellant from civil or criminal liability, and may be reopened at any time if it was procured by fraud or similar fault. In addition, the decision may be reopened within 180 calendar days from the date of the decision for good cause. Good cause exists when there is new and material evidence that was not available or known at the time of the decision and may result in a different conclusion, or when the evidence that was considered clearly shows on its face that an obvious error was made at the time of the decision.

What if I disagree with the decision?

If you disagree with the decision, you may file an appeal with the Medicare Appeals Council. Other parties may also appeal the decision. In addition, the Medicare Appeals Council may decide to review the decision on its own motion. If no party appeals the decision and the Medicare Appeals Council does not review the decision, the decision is binding on all parties and you and the other parties will not have the right to ask a federal court to review the decision.

If you are not already represented, you may appoint an attorney or other person to represent you.

How much time do I have to file an appeal?

The Medicare Appeals Council must receive your written appeal **within 60 calendar days** of the date that you receive this notice. The Medicare Appeals Council assumes you received this notice 5 calendar days after the date of the notice unless you show that you did not receive it within the 5-day period.

The Medicare Appeals Council will dismiss a late request for review unless you show that you had a good reason for not filing it on time.

How do I file an appeal?

To appeal, you must ask the Medicare Appeals Council to review the decision. Your appeal must be in writing, except that a request for expedited review of a Part D decision may be made orally as described below. Your appeal must identify the parts of the decision that you disagree with, and explain why you disagree.

You may submit a written request for review to the Medicare Appeals Council using one of three available methods: mail, fax, or electronic filing (E-File). **Please do not submit your request for review using more than one method.** Regardless of how you file your appeal, **you must always send a copy of your written request for review to the other parties who received a copy of the decision.**

If you are filing a written request for review, you may use the enclosed *Request for Review* (form DAB-101), or you may write a letter containing the following:

- The beneficiary's/enrollee's name (and telephone number for Part D appeals);
- The beneficiary's/enrollee's Medicare number (Health Insurance Claim Number or Medicare Beneficiary Identifier);
- The item(s), service(s), or specific Part D drug(s) in dispute;
- The specific date(s) the item(s) or service(s) were provided, if applicable;
- For Part D appeals, the plan name;
- For Part D appeals, the OMHA Appeal Number on the adjudicator's decision;
- For Part D appeals requesting expedited review, a statement that you are requesting expedited review;
- The date of the adjudicator's decision (not required for Part D appeals); and
- Your name and signature, and, if applicable, the name and signature of your representative.

Filing by mail:

Mail your appeal and a copy of the enclosed decision to:

Department of Health and Human Services
Departmental Appeals Board
Medicare Appeals Council, MS 6127
Cohen Building Room G-644
330 Independence Ave., S.W.
Washington, D.C. 20201

Filing by fax:

Fax your appeal and a copy of the enclosed decision to (202) 565-0227.

Filing by computer:

Using your web browser, visit the Medicare Operations Division Electronic Filing System (MOD E-File) website at <https://dab.efile.hhs.gov/mod>.

To file a new appeal using MOD E-File, you will need to register by:

- (1) Clicking **Register** on the MOD E-File home page;
- (2) Entering the information requested on the “Register New Account” form; and
- (3) Clicking **Register Account** at the bottom of the form.

You will use the email address and password you provided during registration to access MOD E-File at <https://dab.efile.hhs.gov/mod/users/new>. You will be able to use MOD E-File to file and access the specific materials for appeals to which you are a party or a party’s representative. You may check the status of any appeal on the website homepage without registering.

Once registered, you may file your appeal by:

- (1) Logging into MOD E-File;
- (2) Clicking the **File New Appeal** menu button on the top right of the screen;
- (3) Selecting the type of appeal you are filing (Request for Review or Request for Escalation); and
- (4) Entering the requested Appeal Information and uploading the requested Appeal Documents on the “File New Appeal – Medicare Operations Division” form. You are required to provide information and documents marked with an asterisk.

At a minimum, the Medicare Appeals Council requires an appellant to file a signed Request for Review and a copy of the enclosed decision. All documents should be submitted in Portable Document Format (PDF) whenever possible. Any document, including a Request for Review, will be deemed to have been filed on a given day, if it is uploaded to MOD E-File on or before 11:59 p.m. EST of that day.

Currently, the documents that may be filed electronically are the:

- (1) Request for Review;
- (2) Appointment of Representative form (OMB Form 0938-0950);
- (3) Copy of Administrative Law Judge or attorney adjudicator decision;
- (4) Memorandum or brief or other written statement in support of your appeal; and
- (5) Request to Withdraw your appeal

No other documents aside from the five (5) listed categories above may be submitted through MOD E-File.

Filing by oral request (for expedited review only):

Oral requests for expedited review of a Part D decision may be made by telephone to (866) 365-8204. You must provide the information listed in the bullet points above and a statement that you are requesting an expedited review within 60 calendar days after receipt of this notice of

decision. The Medicare Appeals Council will document the oral request in writing and maintain the documentation in the case file.

Please note that your request for review will only be expedited if (1) the appeal involves an issue specified in 42 C.F.R. § 423.566(b), but does not include solely a request for payment of a Part D drug that has already been furnished, and (2) the prescribing physician (or other prescriber) indicates, or the Medicare Appeals Council determines, that the standard time frame may seriously jeopardize your life, health, or ability to regain maximum function.

How will the Medicare Appeals Council respond to my appeal?

The Medicare Appeals Council will limit its review to the issues raised in the appeal, unless the appeal is filed by an unrepresented beneficiary/enrollee. It may change the parts of the decision that you agree with. It may adopt, modify, or reverse the decision, in whole or in part, or it may send the case back to OMHA for further action. It may also dismiss your appeal.

Questions?

You may call or write our office. A toll-free phone number and mailing address are at the top of this notice.

Additional information about filing an appeal with the Medicare Appeals Council is available at <http://www.hhs.gov/dab/>. You can also call the Medicare Appeals Council's staff in the Medicare Operations Division of the Departmental Appeals Board at (202) 565-0100 or (866) 365-8204 (toll free), if you have questions about filing an appeal.

cc:

DEBRA M PARRISH
788 WASHINGTON RD
PITTSBURGH, PA 15228

C2C Innovative Solutions, Inc.
DME QIC Appeals—ALJ
P.O. Box 44006
Jacksonville, FL 32231-4006

NOVOCURE INC.
195 Commerce Way
Portsmouth, NH 03801

MAXIMUS
DME QIC Appeals—ALJ
3750 Monroe Avenue
Pittsford, NY 14534-1302

Enclosures:

OMHA-152, Decision
DAB-101, Request for Review

REQUEST FOR REVIEW OF ADMINISTRATIVE LAW JUDGE (ALJ) MEDICARE DECISION / DISMISSAL

1. APPELLANT (the party requesting review)

2. ALJ APPEAL NUMBER (on the decision or dismissal)

3. BENEFICIARY*

4. HEALTH INSURANCE CLAIM NUMBER (HICN)*

*If the request involves multiple claims or multiple beneficiaries, attach a list of beneficiaries, HICNs, or other information to identify all claims being appealed.

5. PROVIDER, PRACTITIONER, OR SUPPLIER

6. SPECIFIC ITEM(S) OR SERVICE(S)

7. Medicare claim type: ☐ Part A ☐ Part B ☐ Part C - Medicare Advantage
☐ Part D - Medicare Prescription Drug Plan ☐ Entitlement/enrollment for Part A or Part B

8. Does this request involve authorization for an item or service that has not yet been furnished?

☐ Yes If Yes, skip to Block 8.
☐ No If No, Specific Dates of Service:

9. If the request involves authorization for a prescription drug under Medicare Part D, would application of the standard appellate timeframe seriously jeopardize the beneficiary's life, health, or ability to regain maximum function (as documented by a physician) such that expedited review is appropriate? ☐ Yes ☐ No

I request that the Medicare Appeals Council review the ALJ's ☐ decision or ☐ dismissal order [check one] dated _____. I disagree with the ALJ's action because (specify the parts of the ALJ's decision or dismissal you disagree with and why you think the ALJ was wrong):

(Attach additional sheets if you need more space)

PLEASE ATTACH A COPY OF THE ALJ DECISION OR DISMISSAL ORDER YOU ARE APPEALING.

| | | | | | |
|-----------------------------------------------------|------------|--------|-----------------------------------------------------------------------------------|------------|--------|
| DATE | | | DATE | | |
| APPELLANT'S SIGNATURE (the party requesting review) | | | REPRESENTATIVE'S SIGNATURE (include signed appointment if not already submitted.) | | |
| PRINT NAME | | | PRINT NAME | | |
| ADDRESS | | | ADDRESS | | |
| CITY, STATE, ZIP CODE | | | CITY, STATE, ZIP CODE | | |
| TELEPHONE NUMBER | FAX NUMBER | E-MAIL | TELEPHONE NUMBER | FAX NUMBER | E-MAIL |

(SEE FURTHER INSTRUCTIONS ON PAGE 2)

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Department of Health and Human Services
OFFICE OF MEDICARE HEARINGS AND APPEALS
Cleveland, Ohio

| | | |
|---------------|-----------------------|------------------------------------------------------------|
| Appeal of: | D. CHRISTENSON | OMHA Appeal No.: 1-8630709341 |
| Beneficiary: | D. CHRISTENSON | Medicare: Part B |
| Medicare No.: | *3639A | Before: Scott M. Watson Administrative Law Judge |

DECISION

After carefully considering the evidence, arguments and testimony presented in the record, an **UNFAVORABLE** decision is entered against the Appellant/Beneficiary, D. Christenson.

Procedural History

The Appellant requested coverage under Medicare Part B of a tumor treatment field therapy (TTFT) device called Optune which was supplied by Novocure, Inc. (Provider) on November 13, 2018, December 3, 2018, and January 3, 2019. A claim for the device was submitted to a Medicare Administrative Contractor (MAC), which was denied initially and upon redetermination. On June 7, 2019, a Qualified Independent Contractor (QIC), C2C Solutions, Inc., issued an unfavorable reconsideration decision.

The Appellant timely filed a request for an Administrative Law Judge (ALJ) hearing. The amount in controversy meets the jurisdictional requirements for a hearing. See 42 C.F.R. §§ 405.1006 and 422.5600(b).

An administrative hearing was held by telephone on August 28, 2019. The Appellant was represented by Attorney Debra Parrish. Timothy Parks, RN, of Novocure also testified on behalf of the Appellant. The relevant CMS contractors were sent notice of the hearing but declined to participate.

All exhibits were admitted into evidence without objection.

Issue

The issue is whether Medicare Part B covers the TTFT device to assist with the treatment/management of the Appellant's recurrent glioblastoma.

Findings of Fact

The following facts are established by the preponderance of the evidence.

1. The Appellant, a 65-year old man, was diagnosed with glioblastoma (“GBM”) in July 2015. He then underwent successful resection, chemotherapy, and radiation therapy to treat his GBM. But in early 2016, post-treatment studies showed a size increase in the GBM. The Appellant’s physician ordered one year of TTFT in combination with temozolomide to treat the recurrent GBM. In February 2017, the Appellant began receiving only TTFT for his recurrent GBM. (Park’s testimony; *See also* Appellant’s pre-hearing brief)
2. On September 19, 2018, the Appellant underwent an MRI of the brain. The image showed that the tumor was stable. (Exh. 2, p. 20).
3. The appeal file includes a “Proposed Local Coverage Determination (LCD): Tumor Treatment Field Therapy (TTFT) (DL34823)” that states that “tumor treatment field therapy (E0766) will be denied as not reasonable and necessary for the treatment of *recurrent* GBM.” (Exh. 5, p. 20).
4. The revised LCD L34823, with an effective date of September 1, 2019, expressly states that TTFT will be denied as not reasonable and necessary for treatment of *recurrent* GBM. The LCD also provides that the DME-MACs received a request to reconsider the decision on recurrent GBM in 2018; however, the requestor, Novocure, did not submit new evidence in support of the revised coverage for recurrent disease. The DME-MACs therefore concluded that the request was invalid.¹

Legal Framework

I. ALJ Review Authority

A. Jurisdiction

An individual who, or an organization that, is dissatisfied with the reconsideration of an adverse organization determination is entitled to a hearing before the Secretary of the Department of Health and Human Services (HHS), provided there is a sufficient amount in controversy and a request for hearing is filed in a timely manner. Social Security Act (Act) § 1859(g)(5); see 42 C.F.R. § 422.600. The request for hearing is timely filed if filed within 60 days of the date of notice of a reconsidered determination. 42 C.F.R. § 422.602.

In implementing this statutory directive, the Secretary delegated authority to administer the nationwide hearings and appeals system for the Medicare program to the Office of Medicare Hearings and Appeals (OMHA). See 70 Fed. Reg. 36386, 36387 (June 23, 2005). ALJs within

¹ *See*

<https://med.noridianmedicare.com/documents/2230703/7218263/Tumor+Treatment+Field+Therapy+%28TTFT%29%20LCD+and+PA/8f195ce1-c8e1-4c92-8578-f2b8996e4507>

OMHA issue the final decisions of the Secretary, except for decisions reviewed by the Medicare Appeals Council.

B. Scope of Review

Medicare Advantage Organization determinations and appeals are governed by the regulations in 42 C.F.R. §§ 422.560 through 422.626. Unless otherwise noted, the ALJ hearing procedures set forth in 42 C.F.R. §§ 405.1000 through 405.1064 apply to Medicare Advantage appeals, to the extent they are appropriate. 42 C.F.R. § 422.562(d).

The issues before the ALJ include all the issues brought out in the initial determination, redetermination, or reconsideration that were not decided entirely in the Appellant's favor. 42 C.F.R. § 405.1032(a). However, if evidence presented before the hearing causes the ALJ to question a favorable portion of the determination, he or she may notify the parties before the hearing and may consider it an issue at the hearing. *Id.*

C. Standard of Review

The OMHA is staffed with ALJs who conduct de novo hearings. 42 C.F.R. § 405.1000(d). A de novo review means the ALJ reviews the evidence without regard to the findings in the prior determinations on the claim and makes an independent assessment based on the evidence and the controlling laws. However, the burden of proving each element of a Medicare claim lies with the appellant and is satisfied by submitting sufficient evidence in accordance with Medicare rules. See e.g., Act §§ 1814(a)(1), 1815(b), and 1833(e); see also 42 C.F.R. §§ 424.5(a)(6), 405.1018, 405.1028, and 405.1030.

II. Principles of Law

A. Statutes and Regulations

Eligibility for Medicare benefits is determined under Title XVIII of the Act, 42 U.S.C. § 1801 et seq., and federal regulations set forth in Title 42 of the Code of Federal Regulations.

According to section 1862(a)(1)(A) of the Act, no payment may be made under Original Medicare for any expenses incurred for items or services that are "not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." See 42 U.S.C. § 1395y(a)(1)(A); see also 42 C.F.R. § 41.115(k)(1).

B. Policy and Guidance

Section 1871(a)(2) of the Act provides that no rule, requirement or statement of policy, other than a national coverage determination (NCD), can establish or change a substantive legal standard governing the scope of the benefits or payment for services under the Medicare program unless promulgated as a regulation by CMS. NCDs promulgated by the Secretary of HHS under the authority of Section 1862(a)(1) of the Act dictate the criteria under which Medicare covers specified services, procedures or supplies. NCDs are binding upon ALJs. 42 C.F.R. § 405.1060(a)(4); see 42 C.F.R. § 405.1060(b)(1) ("An ALJ may not disregard, set aside or otherwise review an NCD").

Although not subject to the force and effect of law, CMS and its contractors issue policies, manuals and guidelines that describe criteria for coverage of selected types of medical items and services in the form of manuals and local coverage determinations (LCDs). 42 C.F.R. § 405.1062 states that an ALJ is not bound by LCDs or CMS program guidance, such as program memoranda and manual instructions, but will give substantial deference to these policies if they are applicable to a particular case. If an ALJ declines to follow a policy in a particular case, the ALJ decision must explain the reasons why the policy was not followed. An ALJ decision to disregard such policy applies only to the specific claim being considered and does not have precedential effect.

The DME MAC with jurisdiction over this appeal applied LCD L34823 (Tumor Treatment Field Therapy (TTFT)). The applicable LCD provides that TTFT (E0766) will be denied as not reasonable and necessary.

Analysis

The Appellant seeks reimbursement for TTFT (E0766) to treat recurrent GBM. The QIC and the MAC denied the request because a Medicare local coverage determination states “[t]umor treatment field therapy (E0766) will be denied as not reasonable and necessary.” (LCD L34823). For the reasons set forth below, I agree with the previous denial and conclude that Medicare Part B does not provide for coverage of TTFT for the treatment of the Appellant’s recurrent GBM.

CMS has determined that the TTFT Optune device (E0766) meets the definition of durable medical equipment (DME). (See Policy Article A52711). Medicare covers DME when sufficient information is provided to conclude that the DME was medically reasonable and necessary for the treatment or management of an illness or medical condition. See Act § 1862(a)(1)(A). Generally, CMS and its contractors publish coverage policies and guidance to apply when considering whether or not certain DME is reasonable and necessary. See Act § 1869(f)(2)(B); 42 C.F.R. § 405.1060; *MPIM*, ch 13, § 13.5.1

In this case, the MAC and the QIC relied on LCD L34823 to support denial of the Appellant’s request for coverage. The pertinent LCD provides conclusory language stating “[t]umor treatment field therapy (E0766) will be denied as not reasonable and necessary.” The LCD does not elaborate further as to why TTFT is deemed not reasonable and necessary.

Since the publication of this LCD, the DME-MACs, through their medical directors, have conceded that LCD L34823 only precludes coverage of TTFT for **recurrent** GBM as not reasonable and necessary. The DME-MACs have explicitly stated that LCD L324823 does not address coverage for **newly diagnosed** GBM. However, the issue in this case pertains to coverage of TTFT for **recurrent** GBM, which is addressed by L34823. I therefore find that L34823 should be applied to find that TTFT for the treatment of recurrent GBM is considered not reasonable and necessary.

While I understand that this treatment has been effective for the Appellant since he began receiving the treatment, I am bound to follow Medicare rules and regulations. I find that there is not sufficient evidence to show that L34823 does not apply to the Beneficiary’s diagnosis, nor is

there sufficient evidence to show that the LCD should be disregarded. Neither the old nor the revised LCD provides for coverage of TTFT for the treatment of recurrent GBM. Therefore, based upon the record, I find that the Appellant is not entitled to coverage of the Optune tumor treatment field therapy (E0766) received on November 13, 2018, December 3, 2018, and January 3, 2019.

Where the Medicare coverage requirements have not been met, waiver of liability pursuant to section 1879(a) of the Social Security Act, 42 U.S.C. § 1395pp(a), might apply. A provider will be held liable for the cost of services unless it did not know, and reasonably could not have known, that the services would not be covered. The same statutory provision applies to beneficiaries, although the “reasonably could not have known” standard is interpreted and applied differently in their case due to their presumed unfamiliarity with the numerous publications that govern Medicare coverage.

There was no Advance Beneficiary Notice (“ABN”) included in the file. The Beneficiary neither knew, nor reasonably should have been expected to know, that services would not be covered by Medicare. Novocure (“Provider”) is presumed to have knowledge of published Medicare coverage rules, regulations, and guidelines. The Provider either knew, or reasonably should have been expected to know, that the services denied would not be covered by Medicare. As a result, the Provider is not eligible for a waiver of liability, pursuant to § 1879 of the Act, 42 U.S.C. § 1395pp(a), and is liable for the non-covered charges.

Conclusions of Law

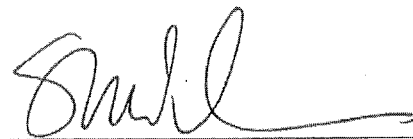
Medicare Part B does not cover the tumor treatment field therapy (E0766) for recurrent GBM; therefore, the Appellant is not entitled to coverage of the TTFT (E0776) provided to the Appellant on November 13, 2018, December 3, 2018, and January 3, 2019.

Novocure remains financially liable for the denied charges.

Order

The Medicare contractor is **DIRECTED** to process the claim in accordance with this decision.

SO ORDERED



Scott M. Watson
Administrative Law Judge

Dated: **SEP 12 2019**



Department of Health and Human Services
OFFICE OF MEDICARE HEARINGS AND APPEALS
Cleveland, Ohio

| | |
|------------------------------------|----------------------------------------------------------------|
| Appeal of: D. CHRISTENSON | OMHA Appeal No.: 1-8630709341 |
| Beneficiary: D. CHRISTENSON | Medicare: Part B |
| Medicare No.: *****3639A | Before: Scott Watson Administrative Law Judge |

EXHIBIT LIST

| EXHIBIT NUMBER | DESCRIPTION | PAGE NUMBERS |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------|-----------------|
| 1 | Initial, Redetermination and Reconsideration Procedural Documents, Articles and literature, Redacted ALJ decisions | 1-3145 |
| 2 | Medical Records/Evidence Received by CMS Contractors | 1-23 |
| 3 | Request for ALJ Hearing / Appointment of representative form (Beneficiary) 6/17/19 Request for ALJ hearing (Novocure) 7/1/19 | 1-12 |
| 4 | OMHA Proceedings Notice of hearing 7/1/19 Response to NOH 7/5/19 | 1-10 |
| 5 | Pre-Hearing Brief (Beneficiary Rep) 7/8/19 | 1-47 |

Dated: August 12, 2019

¹ Some materials in the exhibited record are dual sided. References to the second side include a notation of (reverse). For example, "Ex. 1, p. 1 (reverse)." The second side of a dual sided page is not included in the page count for the page number range.



Department of Health and Human Services
Office of the Secretary

OFFICE OF MEDICARE HEARINGS AND APPEALS

Cleveland Field Office
200 Public Square, Suite 1300
Cleveland, OH 44114-2316
216-615-4000 (Main)
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216-615-6735 (Fax)
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Date: September 12, 2019

D. CHRISTENSON
5754 CLEVEDON LN
OSHKOSH, WI 54904-9729

NOTICE OF DECISION

Appellant: D. CHRISTENSON
OMHA Appeal Number: 1-8630709341

Enclosed is the decision for the above case. This decision is based on the administrative record, including any evidence or testimony presented at the hearing, if one was held. The decision is not precedential, does not release the appellant from civil or criminal liability, and may be reopened at any time if it was procured by fraud or similar fault. In addition, the decision may be reopened within 180 calendar days from the date of the decision for good cause. Good cause exists when there is new and material evidence that was not available or known at the time of the decision and may result in a different conclusion, or when the evidence that was considered clearly shows on its face that an obvious error was made at the time of the decision.

What if I disagree with the decision?

If you disagree with the decision, you may file an appeal with the Medicare Appeals Council. Other parties may also appeal the decision. In addition, the Medicare Appeals Council may decide to review the decision on its own motion. If no party appeals the decision and the Medicare Appeals Council does not review the decision, the decision is binding on all parties and you and the other parties will not have the right to ask a federal court to review the decision.

If you are not already represented, you may appoint an attorney or other person to represent you.

How much time do I have to file an appeal?

The Medicare Appeals Council must receive your written appeal **within 60 calendar days** of the date that you receive this notice. The Medicare Appeals Council assumes you received this notice 5 calendar days after the date of the notice unless you show that you did not receive it within the 5-day period.

The Medicare Appeals Council will dismiss a late request for review unless you show that you had a good reason for not filing it on time.

How do I file an appeal?

To appeal, you must ask the Medicare Appeals Council to review the decision. Your appeal must be in writing, except that a request for expedited review of a Part D decision may be made orally as described below. Your appeal must identify the parts of the decision that you disagree with, and explain why you disagree.

You may submit a written request for review to the Medicare Appeals Council using one of three available methods: mail, fax, or electronic filing (E-File). **Please do not submit your request for review using more than one method.** Regardless of how you file your appeal, **you must always send a copy of your written request for review to the other parties who received a copy of the decision.**

If you are filing a written request for review, you may use the enclosed *Request for Review* (form DAB-101), or you may write a letter containing the following:

- The beneficiary's/enrollee's name (and telephone number for Part D appeals);
- The beneficiary's/enrollee's Medicare number (Health Insurance Claim Number or Medicare Beneficiary Identifier);
- The item(s), service(s), or specific Part D drug(s) in dispute;
- The specific date(s) the item(s) or service(s) were provided, if applicable;
- For Part D appeals, the plan name;
- For Part D appeals, the OMHA Appeal Number on the adjudicator's decision;
- For Part D appeals requesting expedited review, a statement that you are requesting expedited review;
- The date of the adjudicator's decision (not required for Part D appeals); and
- Your name and signature, and, if applicable, the name and signature of your representative.

Filing by mail:

Mail your appeal and a copy of the enclosed decision to:

Department of Health and Human Services
Departmental Appeals Board
Medicare Appeals Council, MS 6127
Cohen Building Room G-644
330 Independence Ave., S.W.
Washington, D.C. 20201

Filing by fax:

Fax your appeal and a copy of the enclosed decision to **(202) 565-0227**.

Filing by computer:

Using your web browser, visit the Medicare Operations Division Electronic Filing System (MOD E-File) website at <https://dab.efile.hhs.gov/mod>.

To file a new appeal using MOD E-File, you will need to register by:

- (1) Clicking **Register** on the MOD E-File home page;
- (2) Entering the information requested on the “Register New Account” form; and
- (3) Clicking **Register Account** at the bottom of the form.

You will use the email address and password you provided during registration to access MOD E-File at <https://dab.efile.hhs.gov/mod/users/new>. You will be able to use MOD E-File to file and access the specific materials for appeals to which you are a party or a party’s representative. You may check the status of any appeal on the website homepage without registering.

Once registered, you may file your appeal by:

- (1) Logging into MOD E-File;
- (2) Clicking the **File New Appeal** menu button on the top right of the screen;
- (3) Selecting the type of appeal you are filing (Request for Review or Request for Escalation); and
- (4) Entering the requested Appeal Information and uploading the requested Appeal Documents on the “File New Appeal – Medicare Operations Division” form. You are required to provide information and documents marked with an asterisk.

At a minimum, the Medicare Appeals Council requires an appellant to file a signed Request for Review and a copy of the enclosed decision. All documents should be submitted in Portable Document Format (PDF) whenever possible. Any document, including a Request for Review, will be deemed to have been filed on a given day, if it is uploaded to MOD E-File on or before 11:59 p.m. EST of that day.

Currently, the documents that may be filed electronically are the:

- (1) Request for Review;
- (2) Appointment of Representative form (OMB Form 0938-0950);
- (3) Copy of Administrative Law Judge or attorney adjudicator decision;
- (4) Memorandum or brief or other written statement in support of your appeal; and
- (5) Request to Withdraw your appeal

No other documents aside from the five (5) listed categories above may be submitted through MOD E-File.

Filing by oral request (for expedited review only):

Oral requests for expedited review of a Part D decision may be made by telephone to **(866) 365-8204**. You must provide the information listed in the bullet points above and a statement that you are requesting an expedited review within 60 calendar days after receipt of this notice of

decision. The Medicare Appeals Council will document the oral request in writing and maintain the documentation in the case file.

Please note that your request for review will only be expedited if (1) the appeal involves an issue specified in 42 C.F.R. § 423.566(b), but does not include solely a request for payment of a Part D drug that has already been furnished, and (2) the prescribing physician (or other prescriber) indicates, or the Medicare Appeals Council determines, that the standard time frame may seriously jeopardize your life, health, or ability to regain maximum function.

How will the Medicare Appeals Council respond to my appeal?

The Medicare Appeals Council will limit its review to the issues raised in the appeal, unless the appeal is filed by an unrepresented beneficiary/enrollee. It may change the parts of the decision that you agree with. It may adopt, modify, or reverse the decision, in whole or in part, or it may send the case back to OMHA for further action. It may also dismiss your appeal.

Questions?

You may call or write our office. A toll-free phone number and mailing address are at the top of this notice.

Additional information about filing an appeal with the Medicare Appeals Council is available at <http://www.hhs.gov/dab/>. You can also call the Medicare Appeals Council's staff in the Medicare Operations Division of the Departmental Appeals Board at (202) 565-0100 or (866) 365-8204 (toll free), if you have questions about filing an appeal.

cc:

DEBRA M PARRISH
788 WASHINGTON RD
PITTSBURGH, PA 15228

C2C Innovative Solutions, Inc.
DME QIC Appeals—ALJ
P.O. Box 44006
Jacksonville, FL 32231-4006

NOVOCURE INC.
195 Commerce Way
Portsmouth, NH 03801

MAXIMUS
DME QIC Appeals—ALJ
3750 Monroe Avenue
Pittsford, NY 14534-1302

Enclosures:

OMHA-152, Decision
DAB-101, Request for Review

REQUEST FOR REVIEW OF ADMINISTRATIVE LAW JUDGE (ALJ) MEDICARE DECISION / DISMISSAL

| | |
|--------------------------------------------|-----------------------------------------------------|
| 1. APPELLANT (the party requesting review) | 2. ALJ APPEAL NUMBER (on the decision or dismissal) |
| 3. BENEFICIARY* | 4. HEALTH INSURANCE CLAIM NUMBER (HICN)* |

*If the request involves multiple claims or multiple beneficiaries, attach a list of beneficiaries, HICNs, or other information to identify all claims being appealed.

| | |
|----------------------------------------|-----------------------------------|
| 5. PROVIDER, PRACTITIONER, OR SUPPLIER | 6. SPECIFIC ITEM(S) OR SERVICE(S) |
|----------------------------------------|-----------------------------------|

| |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 7. Medicare claim type: <input type="checkbox"/> Part A <input type="checkbox"/> Part B <input type="checkbox"/> Part C - Medicare Advantage <input type="checkbox"/> Part D - Medicare Prescription Drug Plan <input type="checkbox"/> Entitlement/enrollment for Part A or Part B |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

8. Does this request involve authorization for an item or service that has not yet been furnished?

- ☐ Yes If Yes, skip to Block 8.
☐ No If No, Specific Dates of Service:

9. If the request involves authorization for a prescription drug under Medicare Part D, would application of the standard appellate timeframe seriously jeopardize the beneficiary's life, health, or ability to regain maximum function (as documented by a physician) such that expedited review is appropriate? ☐ Yes ☐ No

I request that the Medicare Appeals Council review the ALJ's ☐ decision or ☐ dismissal order [check one] dated _____. I disagree with the ALJ's action because (specify the parts of the ALJ's decision or dismissal you disagree with and why you think the ALJ was wrong):

(Attach additional sheets if you need more space)

PLEASE ATTACH A COPY OF THE ALJ DECISION OR DISMISSAL ORDER YOU ARE APPEALING.

| | | | | | |
|-----------------------------------------------------|------------|--------|-----------------------------------------------------------------------------------|------------|--------|
| DATE | | | DATE | | |
| APPELLANT'S SIGNATURE (the party requesting review) | | | REPRESENTATIVE'S SIGNATURE (include signed appointment if not already submitted.) | | |
| PRINT NAME | | | PRINT NAME | | |
| ADDRESS | | | ADDRESS | | |
| CITY, STATE, ZIP CODE | | | CITY, STATE, ZIP CODE | | |
| TELEPHONE NUMBER | FAX NUMBER | E-MAIL | TELEPHONE NUMBER | FAX NUMBER | E-MAIL |

(SEE FURTHER INSTRUCTIONS ON PAGE 2)

If you have additional evidence, submit it with this request for review. If you need more time, you must request an extension of time in writing now, explaining why you are unable to submit the evidence or legal argument now.

If you are a provider, supplier, or a beneficiary represented by a provider or supplier, and your case was reconsidered by a Qualified Independent Contractor (QIC), the Medicare Appeals Council will not consider new evidence related to issues the QIC has already considered unless you show that you have a good reason for submitting it for the first time to the Medicare Appeals Council.

IMPORTANT: Include the HICN and ALJ Appeal Number on any letter or other material you submit.

This request must be received within 60 calendar days after you receive the ALJ's decision or dismissal, unless we extend the time limit for good cause. We assume you received the decision or dismissal 5 calendar days after it was issued, unless you show you received it later. If this request will not be received within 65 calendar days from the date on the decision or dismissal order, please explain why on a separate sheet.

You must file your request for review in writing with the Medicare Appeals Council at:

Department of Health and Human Services
Departmental Appeals Board
Medicare Appeals Council, MS 6127
Cohen Building Room G-644
330 Independence Ave., S.W.
Washington, D.C. 20201

You may send the request for review by U.S. Mail, a common carrier such as FedEx, or by fax to (202) 565-0227. If you send a fax, please do not also mail a copy. **You must send a copy of your appeal to the other parties and indicate that all parties, to include all beneficiaries, have been copied on the request for review. For claims involving multiple beneficiaries, you may submit a copy of the cover letters issued or a spreadsheet of the beneficiaries and addresses who received a copy of the request for review.**

If you have any questions about your request for review or wish to request expedited review of a claim involving authorization of your prescription drug under Medicare Part D, you may call the Medicare Appeals Council's staff in the Medicare Operations Division of the Departmental Appeals Board at (202) 565-0100. You may also visit our web site at www.hhs.gov/dab for additional information on how to file your request for review.

PRIVACY ACT STATEMENT

The collection of information on this form is authorized by the Social Security Act (section 205(a) of title II, section 702 of title VII, section 1155 of Title XI, and sections 1852(g)(5), 1869(b)(1), 1871, 1872, and 1876(c)(5)(B) of title XVIII, as appropriate). The information provided will be used to further document your claim. Information requested on this form is voluntary, but failure to provide all or any part of the requested information may affect the determination of your claim. Information you furnish on this form may be disclosed by the Department of Health and Human Services or the Social Security Administration to another person or governmental agency only with respect to programs under the Social Security Act and to comply with Federal laws requiring the disclosure of information or the exchange of information between the Department of Health and Human Services, the Social Security Administration, or other agencies.



Department of Health and Human Services
OFFICE OF MEDICARE HEARINGS AND APPEALS
Cleveland, Ohio

| | | |
|---------------|-----------------------|------------------------------------------------------------|
| Appeal of: | D. CHRISTENSON | OMHA Appeal No.: 1-8630709341 |
| Beneficiary: | D. CHRISTENSON | Medicare: Part B |
| Medicare No.: | *3639A | Before: Scott M. Watson Administrative Law Judge |

DECISION

After carefully considering the evidence, arguments and testimony presented in the record, an **UNFAVORABLE** decision is entered against the Appellant/Beneficiary, D. Christenson.

Procedural History

The Appellant requested coverage under Medicare Part B of a tumor treatment field therapy (TTFT) device called Optune which was supplied by Novocure, Inc. (Provider) on November 13, 2018, December 3, 2018, and January 3, 2019. A claim for the device was submitted to a Medicare Administrative Contractor (MAC), which was denied initially and upon redetermination. On June 7, 2019, a Qualified Independent Contractor (QIC), C2C Solutions, Inc., issued an unfavorable reconsideration decision.

The Appellant timely filed a request for an Administrative Law Judge (ALJ) hearing. The amount in controversy meets the jurisdictional requirements for a hearing. See 42 C.F.R. §§ 405.1006 and 422.5600(b).

An administrative hearing was held by telephone on August 28, 2019. The Appellant was represented by Attorney Debra Parrish. Timothy Parks, RN, of Novocure also testified on behalf of the Appellant. The relevant CMS contractors were sent notice of the hearing but declined to participate.

All exhibits were admitted into evidence without objection.

Issue

The issue is whether Medicare Part B covers the TTFT device to assist with the treatment/management of the Appellant's recurrent glioblastoma.

Findings of Fact

The following facts are established by the preponderance of the evidence.

1. The Appellant, a 65-year old man, was diagnosed with glioblastoma (“GBM”) in July 2015. He then underwent successful resection, chemotherapy, and radiation therapy to treat his GBM. But in early 2016, post-treatment studies showed a size increase in the GBM. The Appellant’s physician ordered one year of TTFT in combination with temozolomide to treat the recurrent GBM. In February 2017, the Appellant began receiving only TTFT for his recurrent GBM. (Park’s testimony; *See* also Appellant’s pre-hearing brief)
2. On September 19, 2018, the Appellant underwent an MRI of the brain. The image showed that the tumor was stable. (Exh. 2, p. 20).
3. The appeal file includes a “Proposed Local Coverage Determination (LCD): Tumor Treatment Field Therapy (TTFT) (DL34823)” that states that “tumor treatment field therapy (E0766) will be denied as not reasonable and necessary for the treatment of *recurrent* GBM.” (Exh. 5, p. 20).
4. The revised LCD L34823, with an effective date of September 1, 2019, expressly states that TTFT will be denied as not reasonable and necessary for treatment of *recurrent* GBM. The LCD also provides that the DME-MACs received a request to reconsider the decision on recurrent GBM in 2018; however, the requestor, Novocure, did not submit new evidence in support of the revised coverage for recurrent disease. The DME-MACs therefore concluded that the request was invalid.¹

Legal Framework

I. ALJ Review Authority

A. Jurisdiction

An individual who, or an organization that, is dissatisfied with the reconsideration of an adverse organization determination is entitled to a hearing before the Secretary of the Department of Health and Human Services (HHS), provided there is a sufficient amount in controversy and a request for hearing is filed in a timely manner. Social Security Act (Act) § 1859(g)(5); see 42 C.F.R. § 422.600. The request for hearing is timely filed if filed within 60 days of the date of notice of a reconsidered determination. 42 C.F.R. § 422.602.

In implementing this statutory directive, the Secretary delegated authority to administer the nationwide hearings and appeals system for the Medicare program to the Office of Medicare Hearings and Appeals (OMHA). See 70 Fed. Reg. 36386, 36387 (June 23, 2005). ALJs within

¹ *See*

<https://med.noridianmedicare.com/documents/2230703/7218263/Tumor+Treatment+Field+Therapy+%28TTFT%29%20LCD+and+PA/8f195ce1-c8e1-4c92-8578-f2b8996e4507>

OMHA issue the final decisions of the Secretary, except for decisions reviewed by the Medicare Appeals Council.

B. Scope of Review

Medicare Advantage Organization determinations and appeals are governed by the regulations in 42 C.F.R. §§ 422.560 through 422.626. Unless otherwise noted, the ALJ hearing procedures set forth in 42 C.F.R. §§ 405.1000 through 405.1064 apply to Medicare Advantage appeals, to the extent they are appropriate. 42 C.F.R. § 422.562(d).

The issues before the ALJ include all the issues brought out in the initial determination, redetermination, or reconsideration that were not decided entirely in the Appellant's favor. 42 C.F.R. § 405.1032(a). However, if evidence presented before the hearing causes the ALJ to question a favorable portion of the determination, he or she may notify the parties before the hearing and may consider it an issue at the hearing. *Id.*

C. Standard of Review

The OMHA is staffed with ALJs who conduct de nova hearings. 42 C.F.R. § 405.1000(d). A de novo review means the ALJ reviews the evidence without regard to the findings in the prior determinations on the claim and makes an independent assessment based on the evidence and the controlling laws. However, the burden of proving each element of a Medicare claim lies with the appellant and is satisfied by submitting sufficient evidence in accordance with Medicare rules. See e.g., Act §§ 1814(a)(1), 1815(b), and 1833(e); see also 42 C.F.R. §§ 424.5(a)(6), 405.1018, 405.1028, and 405.1030.

II. Principles of Law

A. Statutes and Regulations

Eligibility for Medicare benefits is determined under Title XVIII of the Act, 42 U.S.C. § 1801 et seq., and federal regulations set forth in Title 42 of the Code of Federal Regulations.

According to section 1862(a)(1)(A) of the Act, no payment may be made under Original Medicare for any expenses incurred for items or services that are "not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." See 42 U.S.C. § 1395y(a)(1)(A); see also 42 C.F.R. § 41.115(k)(1).

B. Policy and Guidance

Section 1871(a)(2) of the Act provides that no rule, requirement or statement of policy, other than a national coverage determination (NCD), can establish or change a substantive legal standard governing the scope of the benefits or payment for services under the Medicare program unless promulgated as a regulation by CMS. NCDs promulgated by the Secretary of HHS under the authority of Section 1862(a)(1) of the Act dictate the criteria under which Medicare covers specified services, procedures or supplies. NCDs are binding upon ALJs. 42 C.F.R. § 405.1060(a)(4); see 42 C.F.R. § 405.1060(b)(1) ("An ALJ may not disregard, set aside or otherwise review an NCD").

Although not subject to the force and effect of law, CMS and its contractors issue policies, manuals and guidelines that describe criteria for coverage of selected types of medical items and services in the form of manuals and local coverage determinations (LCDs). 42 C.F.R. § 405.1062 states that an ALJ is not bound by LCDs or CMS program guidance, such as program memoranda and manual instructions, but will give substantial deference to these policies if they are applicable to a particular case. If an ALJ declines to follow a policy in a particular case, the ALJ decision must explain the reasons why the policy was not followed. An ALJ decision to disregard such policy applies only to the specific claim being considered and does not have precedential effect.

The DME MAC with jurisdiction over this appeal applied LCD L34823 (Tumor Treatment Field Therapy (TTFT)). The applicable LCD provides that TTFT (E0766) will be denied as not reasonable and necessary.

Analysis

The Appellant seeks reimbursement for TTFT (E0766) to treat recurrent GBM. The QIC and the MAC denied the request because a Medicare local coverage determination states “[t]umor treatment field therapy (E0766) will be denied as not reasonable and necessary.” (LCD L34823). For the reasons set forth below, I agree with the previous denial and conclude that Medicare Part B does not provide for coverage of TTFT for the treatment of the Appellant’s recurrent GBM.

CMS has determined that the TTFT Optune device (E0766) meets the definition of durable medical equipment (DME). (See Policy Article A52711). Medicare covers DME when sufficient information is provided to conclude that the DME was medically reasonable and necessary for the treatment or management of an illness or medical condition. See Act § 1862(a)(1)(A). Generally, CMS and its contractors publish coverage policies and guidance to apply when considering whether or not certain DME is reasonable and necessary. See Act § 1869(f)(2)(B); 42 C.F.R. § 405.1060; *MPIM*, ch 13, § 13.5.1

In this case, the MAC and the QIC relied on LCD L34823 to support denial of the Appellant’s request for coverage. The pertinent LCD provides conclusory language stating “[t]umor treatment field therapy (E0766) will be denied as not reasonable and necessary.” The LCD does not elaborate further as to why TTFT is deemed not reasonable and necessary.

Since the publication of this LCD, the DME-MACs, through their medical directors, have conceded that LCD L34823 only precludes coverage of TTFT for **recurrent** GBM as not reasonable and necessary. The DME-MACs have explicitly stated that LCD L324823 does not address coverage for **newly diagnosed** GBM. However, the issue in this case pertains to coverage of TTFT for **recurrent** GBM, which is addressed by L34823. I therefore find that L34823 should be applied to find that TTFT for the treatment of recurrent GBM is considered not reasonable and necessary.

While I understand that this treatment has been effective for the Appellant since he began receiving the treatment, I am bound to follow Medicare rules and regulations. I find that there is not sufficient evidence to show that L34823 does not apply to the Beneficiary’s diagnosis, nor is

there sufficient evidence to show that the LCD should be disregarded. Neither the old nor the revised LCD provides for coverage of TTFT for the treatment of recurrent GBM. Therefore, based upon the record, I find that the Appellant is not entitled to coverage of the Optune tumor treatment field therapy (E0766) received on November 13, 2018, December 3, 2018, and January 3, 2019.

Where the Medicare coverage requirements have not been met, waiver of liability pursuant to section 1879(a) of the Social Security Act, 42 U.S.C. § 1395pp(a), might apply. A provider will be held liable for the cost of services unless it did not know, and reasonably could not have known, that the services would not be covered. The same statutory provision applies to beneficiaries, although the “reasonably could not have known” standard is interpreted and applied differently in their case due to their presumed unfamiliarity with the numerous publications that govern Medicare coverage.

There was no Advance Beneficiary Notice (“ABN”) included in the file. The Beneficiary neither knew, nor reasonably should have been expected to know, that services would not be covered by Medicare. Novocure (“Provider”) is presumed to have knowledge of published Medicare coverage rules, regulations, and guidelines. The Provider either knew, or reasonably should have been expected to know, that the services denied would not be covered by Medicare. As a result, the Provider is not eligible for a waiver of liability, pursuant to § 1879 of the Act, 42 U.S.C. § 1395pp(a), and is liable for the non-covered charges.

Conclusions of Law

Medicare Part B does not cover the tumor treatment field therapy (E0766) for recurrent GBM; therefore, the Appellant is not entitled to coverage of the TTFT (E0776) provided to the Appellant on November 13, 2018, December 3, 2018, and January 3, 2019.

Novocure remains financially liable for the denied charges.

Order

The Medicare contractor is **DIRECTED** to process the claim in accordance with this decision.

SO ORDERED



Scott M. Watson
Administrative Law Judge

Dated: SEP 12 2019



**Department of Health and Human Services
OFFICE OF MEDICARE HEARINGS AND APPEALS
Cleveland, Ohio**

Appeal of: **D. CHRISTENSON**

OMHA Appeal No.: **1-8630709341**

Beneficiary: **D. CHRISTENSON**

Medicare: **Part B**

Medicare No.: *******3639A**

Before: **Scott Watson
Administrative Law Judge**

EXHIBIT LIST

| EXHIBIT NUMBER | DESCRIPTION | PAGE NUMBERS |
|---------------------------|---------------------------------------------------------------------------------------------------------------------------------|-------------------------|
| 1 | Initial, Redetermination and Reconsideration Procedural Documents, Articles and literature, Redacted ALJ decisions | 1-3145 |
| 2 | Medical Records/Evidence Received by CMS Contractors | 1-23 |
| 3 | Request for ALJ Hearing / Appointment of representative form (Beneficiary) 6/17/19 Request for ALJ hearing (Novocure) 7/1/19 | 1-12 |
| 4 | OMHA Proceedings Notice of hearing 7/1/19 Response to NOH 7/5/19 | 1-10 |
| 5 | Pre-Hearing Brief (Beneficiary Rep) 7/8/19 | 1-47 |

Dated: August 12, 2019

¹ Some materials in the exhibited record are dual sided. References to the second side include a notation of (reverse). For example, "Ex. 1, p. 1 (reverse)." The second side of a dual sided page is not included in the page count for the page number range.

IMAGE REQUEST

INDEX UNDER APPEAL NUMBER

1 - 8630709341

IMAGE UNDER:

ALJ DECISION LETTER (DL)..... ☐

AMENDED: ☐

APPELLANT CORRESPONDENCE (AC)...☐

CASE FILE – FOR MAC/DAB (CF).....☒

MAC/DAB DECISION LETTER (DD)..... ☐

AMENDED: ☐

OMR REFERRAL (OR).... ☐

REFERRAL VERIFICATION (RV).....☐

DAB REQUEST FORM (DRF)..... ☐

JIMMO.....☐

SPECIAL SCAN REQUESTS:

DATE NEEDED BY: _____ RETURN TO: _____

Search Docket

Docket Number: M-19-2981**Received****OCT 03 2019****Appeal Information****ADQIC-RECORDS MGMT****Appellant**

Novocure

ALJ Appeal Number(s)

1-8630709341

Beneficiary Name

David Christenson

Last 4 digits of the HICN

3639

HIC Suffix

A

All uploaded documents should be in PDF, MICROSOFT OFFICE, AUDIO or VIDEO format and cannot exceed 5 GB in size.

**DRAG AND DROP TO UPLOAD****Contractor Uploads**

| # | Document Name | Uploaded By | Date Uploaded |
|---|---------------|-------------|---------------|
|---|---------------|-------------|---------------|

E-Filed Documents

| # | Document Name | Document Type | Date Uploaded |
|---|------------------------------------------|-----------------------------------|------------------------|
| 1 | 1013346_MAC_Request_Form.pdf [178 KB] | Request for Review (Form DAB-101) | 09/26/2019 09:54 am |



Department of Health and Human Services
OFFICE OF MEDICARE HEARINGS AND APPEALS
Central Operations Division

Initials - OMHA
ASPW

| | | |
|---------------------------------------------------------------------|--------------------------------------------------------|----------------|
| OMHA Contact: Charles Reich Phone: 216-615-7040 | QIC: B - DME | QIC Date Stamp |
| OMHA Contact: Denise Rydzewski Phone: 216-615-4028 | QIC Contact: Ivonne Feria | |
| Fax: 216-615-6730 | Phone: 904-224-7380 Fax: 904-224-2750 | |

OMHA RECONSIDERATION CASE FILE REQUEST FORM

The Office of Medicare Hearings and Appeals (OMHA) received a Request for Hearing for the following:

| | | | | |
|---------------------------------------------------------------------------------------------------|---------------------------------------|-----------------------|--------------------------|--------|
| **TO QIC** Please check box if case file was sent to ADQIC <input type="checkbox"/> | ALJ Deadline Date | Appellant Name | ALJ Appeal Number | |
| | DL 9/16/2019 QIC# 1-8486340738 | CHRISTENSON | ALJ# 1-8630709341 | |
| | QIC Appeal Number | Beneficiary Last Name | HICN | CLAIMS |

Please staple this request to the case file and send the complete case file(s) to:

OMHA- CLEVELAND FIELD OFFICE
ATTN: INTAKE DEPT.
200 Public Square Suite: 1300
Cleveland, OH 44114



JUDGE SCOTT WATSON

W5CM

Your prompt attention is required in order to avoid any delays in the adjudication of this appeal.
Please fax Acknowledgement to (216) 615-6730.

| | | |
|--------------------------|-----------------------|-----------------------|
| First Request | Second Request | Ad-QIC Request |
| Date: JUN 18 2019 | Date: | Date: |

QIC PROBLEM RESOLUTION
Please check the appropriate box

☐ Decision was rendered by another QIC (check box):

- ☐ Maximus Part A East
- ☐ Maximus Part A West
- ☐ B - South
- ☐ B - North

☐ Case file has already shipped to OMHA

☐ Invalid QIC number

☐ QIC # does not match ALJ #

☐ Beneficiary does not match appeal #

☐ Other _____

Ad-QIC PROBLEM RESOLUTION
Please check the appropriate box

☒ Case file is in transit from QIC

☐ Case file is in storage & will be forwarded to OMHA

☐ Ad-QIC has not received case file

☐ Other _____

Ad-QIC/2nd Request QIC DATE STAMP

RECEIVED
JUN 25 2019
BY: _____



Department of Health and Human Services
OFFICE OF MEDICARE HEARINGS AND APPEALS
Cleveland, Ohio

Received

SEP 20 2019

ADQIC-RECORDS MGMT

Appeal of: **D. CHRISTENSON**

OMHA Appeal No.: **1-8630709341**

Beneficiary: **D. CHRISTENSON**

Medicare: **Part B**

Medicare No.: ***3639A**

Before: **Scott M. Watson**
Administrative Law Judge

DECISION

After carefully considering the evidence, arguments and testimony presented in the record, an **UNFAVORABLE** decision is entered against the Appellant/Beneficiary, D. Christenson.

Procedural History

The Appellant requested coverage under Medicare Part B of a tumor treatment field therapy (TTFT) device called Optune which was supplied by Novocure, Inc. (Provider) on November 13, 2018, December 3, 2018, and January 3, 2019. A claim for the device was submitted to a Medicare Administrative Contractor (MAC), which was denied initially and upon redetermination. On June 7, 2019, a Qualified Independent Contractor (QIC), C2C Solutions, Inc., issued an unfavorable reconsideration decision.

The Appellant timely filed a request for an Administrative Law Judge (ALJ) hearing. The amount in controversy meets the jurisdictional requirements for a hearing. See 42 C.F.R. §§ 405.1006 and 422.5600(b).

An administrative hearing was held by telephone on August 28, 2019. The Appellant was represented by Attorney Debra Parrish. Timothy Parks, RN, of Novocure also testified on behalf of the Appellant. The relevant CMS contractors were sent notice of the hearing but declined to participate.

All exhibits were admitted into evidence without objection.

Issue

The issue is whether Medicare Part B covers the TTFT device to assist with the treatment/management of the Appellant's recurrent glioblastoma.

Findings of Fact

The following facts are established by the preponderance of the evidence.

1. The Appellant, a 65-year old man, was diagnosed with glioblastoma (“GBM”) in July 2015. He then underwent successful resection, chemotherapy, and radiation therapy to treat his GBM. But in early 2016, post-treatment studies showed a size increase in the GBM. The Appellant’s physician ordered one year of TTFT in combination with temozolomide to treat the recurrent GBM. In February 2017, the Appellant began receiving only TTFT for his recurrent GBM. (Park’s testimony; *See* also Appellant’s pre-hearing brief)
2. On September 19, 2018, the Appellant underwent an MRI of the brain. The image showed that the tumor was stable. (Exh. 2, p. 20).
3. The appeal file includes a “Proposed Local Coverage Determination (LCD): Tumor Treatment Field Therapy (TTFT) (DL34823)” that states that “tumor treatment field therapy (E0766) will be denied as not reasonable and necessary for the treatment of *recurrent* GBM.” (Exh. 5, p. 20).
4. The revised LCD L34823, with an effective date of September 1, 2019, expressly states that TTFT will be denied as not reasonable and necessary for treatment of *recurrent* GBM. The LCD also provides that the DME-MACs received a request to reconsider the decision on recurrent GBM in 2018; however, the requestor, Novocure, did not submit new evidence in support of the revised coverage for recurrent disease. The DME-MACs therefore concluded that the request was invalid.¹

Legal Framework

I. ALJ Review Authority

A. Jurisdiction

An individual who, or an organization that, is dissatisfied with the reconsideration of an adverse organization determination is entitled to a hearing before the Secretary of the Department of Health and Human Services (HHS), provided there is a sufficient amount in controversy and a request for hearing is filed in a timely manner. Social Security Act (Act) § 1859(g)(5); see 42 C.F.R. § 422.600. The request for hearing is timely filed if filed within 60 days of the date of notice of a reconsidered determination. 42 C.F.R. § 422.602.

In implementing this statutory directive, the Secretary delegated authority to administer the nationwide hearings and appeals system for the Medicare program to the Office of Medicare Hearings and Appeals (OMHA). See 70 Fed. Reg. 36386, 36387 (June 23, 2005). ALJs within

¹ See <https://med.noridianmedicare.com/documents/2230703/7218263/Tumor+Treatment+Field+Therapy+%28TTFT%29%20LCD+and+PA/8f195ce1-c8e1-4c92-8578-f2b8996e4507>

OMHA issue the final decisions of the Secretary, except for decisions reviewed by the Medicare Appeals Council.

B. Scope of Review

Medicare Advantage Organization determinations and appeals are governed by the regulations in 42 C.F.R. §§ 422.560 through 422.626. Unless otherwise noted, the ALJ hearing procedures set forth in 42 C.F.R. §§ 405.1000 through 405.1064 apply to Medicare Advantage appeals, to the extent they are appropriate. 42 C.F.R. § 422.562(d).

The issues before the ALJ include all the issues brought out in the initial determination, redetermination, or reconsideration that were not decided entirely in the Appellant's favor. 42 C.F.R. § 405.1032(a). However, if evidence presented before the hearing causes the ALJ to question a favorable portion of the determination, he or she may notify the parties before the hearing and may consider it an issue at the hearing. *Id.*

C. Standard of Review

The OMHA is staffed with ALJs who conduct de novo hearings. 42 C.F.R. § 405.1000(d). A de novo review means the ALJ reviews the evidence without regard to the findings in the prior determinations on the claim and makes an independent assessment based on the evidence and the controlling laws. However, the burden of proving each element of a Medicare claim lies with the appellant and is satisfied by submitting sufficient evidence in accordance with Medicare rules. See e.g., Act §§ 1814(a)(1), 1815(b), and 1833(e); see also 42 C.F.R. §§ 424.5(a)(6), 405.1018, 405.1028, and 405.1030.

II. Principles of Law

A. Statutes and Regulations

Eligibility for Medicare benefits is determined under Title XVIII of the Act, 42 U.S.C. § 1801 et seq., and federal regulations set forth in Title 42 of the Code of Federal Regulations.

According to section 1862(a)(1)(A) of the Act, no payment may be made under Original Medicare for any expenses incurred for items or services that are "not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." See 42 U.S.C. § 1395y(a)(1)(A); see also 42 C.F.R. § 411.15(k)(1).

B. Policy and Guidance

Section 1871(a)(2) of the Act provides that no rule, requirement or statement of policy, other than a national coverage determination (NCD), can establish or change a substantive legal standard governing the scope of the benefits or payment for services under the Medicare program unless promulgated as a regulation by CMS. NCDs promulgated by the Secretary of HHS under the authority of Section 1862(a)(1) of the Act dictate the criteria under which Medicare covers specified services, procedures or supplies. NCDs are binding upon ALJs. 42 C.F.R. § 405.1060(a)(4); see 42 C.F.R. § 405.1060(b)(1) ("An ALJ may not disregard, set aside or otherwise review an NCD").

Although not subject to the force and effect of law, CMS and its contractors issue policies, manuals and guidelines that describe criteria for coverage of selected types of medical items and services in the form of manuals and local coverage determinations (LCDs). 42 C.F.R. § 405.1062 states that an ALJ is not bound by LCDs or CMS program guidance, such as program memoranda and manual instructions, but will give substantial deference to these policies if they are applicable to a particular case. If an ALJ declines to follow a policy in a particular case, the ALJ decision must explain the reasons why the policy was not followed. An ALJ decision to disregard such policy applies only to the specific claim being considered and does not have precedential effect.

The DME MAC with jurisdiction over this appeal applied LCD L34823 (Tumor Treatment Field Therapy (TTFT)). The applicable LCD provides that TTFT (E0766) will be denied as not reasonable and necessary.

Analysis

The Appellant seeks reimbursement for TTFT (E0766) to treat recurrent GBM. The QIC and the MAC denied the request because a Medicare local coverage determination states “[t]umor treatment field therapy (E0766) will be denied as not reasonable and necessary.” (LCD L34823). For the reasons set forth below, I agree with the previous denial and conclude that Medicare Part B does not provide for coverage of TTFT for the treatment of the Appellant’s recurrent GBM.

CMS has determined that the TTFT Optune device (E0766) meets the definition of durable medical equipment (DME). (See Policy Article A52711). Medicare covers DME when sufficient information is provided to conclude that the DME was medically reasonable and necessary for the treatment or management of an illness or medical condition. See Act § 1862(a)(1)(A). Generally, CMS and its contractors publish coverage policies and guidance to apply when considering whether or not certain DME is reasonable and necessary. See Act § 1869(f)(2)(B); 42 C.F.R. § 405.1060; *MPIM*, ch 13, § 13.5.1

In this case, the MAC and the QIC relied on LCD L34823 to support denial of the Appellant’s request for coverage. The pertinent LCD provides conclusory language stating “[t]umor treatment field therapy (E0766) will be denied as not reasonable and necessary.” The LCD does not elaborate further as to why TTFT is deemed not reasonable and necessary.

Since the publication of this LCD, the DME-MACs, through their medical directors, have conceded that LCD L34823 only precludes coverage of TTFT for *recurrent* GBM as not reasonable and necessary. The DME-MACs have explicitly stated that LCD L34823 does not address coverage for *newly diagnosed* GBM. However, the issue in this case pertains to coverage of TTFT for *recurrent* GBM, which is addressed by L34823. I therefore find that L34823 should be applied to find that TTFT for the treatment of recurrent GBM is considered not reasonable and necessary.

While I understand that this treatment has been effective for the Appellant since he began receiving the treatment, I am bound to follow Medicare rules and regulations. I find that there is not sufficient evidence to show that L34823 does not apply to the Beneficiary’s diagnosis, nor is

there sufficient evidence to show that the LCD should be disregarded. Neither the old nor the revised LCD provides for coverage of TTFT for the treatment of recurrent GBM. Therefore, based upon the record, I find that the Appellant is not entitled to coverage of the Optune tumor treatment field therapy (E0766) received on November 13, 2018, December 3, 2018, and January 3, 2019.

Where the Medicare coverage requirements have not been met, waiver of liability pursuant to section 1879(a) of the Social Security Act, 42 U.S.C. § 1395pp(a), might apply. A provider will be held liable for the cost of services unless it did not know, and reasonably could not have known, that the services would not be covered. The same statutory provision applies to beneficiaries, although the “reasonably could not have known” standard is interpreted and applied differently in their case due to their presumed unfamiliarity with the numerous publications that govern Medicare coverage.

There was no Advance Beneficiary Notice (“ABN”) included in the file. The Beneficiary neither knew, nor reasonably should have been expected to know, that services would not be covered by Medicare. Novocure (“Provider”) is presumed to have knowledge of published Medicare coverage rules, regulations, and guidelines. The Provider either knew, or reasonably should have been expected to know, that the services denied would not be covered by Medicare. As a result, the Provider is not eligible for a waiver of liability, pursuant to § 1879 of the Act, 42 U.S.C. § 1395pp(a), and is liable for the non-covered charges.

Conclusions of Law

Medicare Part B does not cover the tumor treatment field therapy (E0766) for recurrent GBM; therefore, the Appellant is not entitled to coverage of the TTFT (E0776) provided to the Appellant on November 13, 2018, December 3, 2018, and January 3, 2019.

Novocure remains financially liable for the denied charges.

Order

The Medicare contractor is **DIRECTED** to process the claim in accordance with this decision.

SO ORDERED



Scott M. Watson
Administrative Law Judge

Dated: **SEP 12 2019**

Received



Department of Health and Human Services
Office of the Secretary

SEP 20 2019

OFFICE OF MEDICARE HEARINGS AND APPEALS

ADJIC-RECORDS MGMT

Cleveland Field Office
200 Public Square, Suite 1300
Cleveland, OH 44114-2316
216-615-4000 (Main)
216-615-7546 (ALJ Watson Team)
216-615-6735 (Fax)
866-236-5089 (Toll Free)

Date: September 12, 2019

D. CHRISTENSON
5754 CLEVEDON LN
OSHKOSH, WI 54904-9729

NOTICE OF DECISION

Appellant: D. CHRISTENSON
OMHA Appeal Number: 1-8630709341

Enclosed is the decision for the above case. This decision is based on the administrative record, including any evidence or testimony presented at the hearing, if one was held. The decision is not precedential, does not release the appellant from civil or criminal liability, and may be reopened at any time if it was procured by fraud or similar fault. In addition, the decision may be reopened within 180 calendar days from the date of the decision for good cause. Good cause exists when there is new and material evidence that was not available or known at the time of the decision and may result in a different conclusion, or when the evidence that was considered clearly shows on its face that an obvious error was made at the time of the decision.

What if I disagree with the decision?

If you disagree with the decision, you may file an appeal with the Medicare Appeals Council. Other parties may also appeal the decision. In addition, the Medicare Appeals Council may decide to review the decision on its own motion. If no party appeals the decision and the Medicare Appeals Council does not review the decision, the decision is binding on all parties and you and the other parties will not have the right to ask a federal court to review the decision.

If you are not already represented, you may appoint an attorney or other person to represent you.

How much time do I have to file an appeal?

The Medicare Appeals Council must receive your written appeal **within 60 calendar days** of the date that you receive this notice. The Medicare Appeals Council assumes you received this notice 5 calendar days after the date of the notice unless you show that you did not receive it within the 5-day period.

The Medicare Appeals Council will dismiss a late request for review unless you show that you had a good reason for not filing it on time.

How do I file an appeal?

To appeal, you must ask the Medicare Appeals Council to review the decision. Your appeal must be in writing, except that a request for expedited review of a Part D decision may be made orally as described below. Your appeal must identify the parts of the decision that you disagree with, and explain why you disagree.

You may submit a written request for review to the Medicare Appeals Council using one of three available methods: mail, fax, or electronic filing (E-File). **Please do not submit your request for review using more than one method.** Regardless of how you file your appeal, **you must always send a copy of your written request for review to the other parties who received a copy of the decision.**

If you are filing a written request for review, you may use the enclosed *Request for Review* (form DAB-101), or you may write a letter containing the following:

- The beneficiary's/enrollee's name (and telephone number for Part D appeals);
- The beneficiary's/enrollee's Medicare number (Health Insurance Claim Number or Medicare Beneficiary Identifier);
- The item(s), service(s), or specific Part D drug(s) in dispute;
- The specific date(s) the item(s) or service(s) were provided, if applicable;
- For Part D appeals, the plan name;
- For Part D appeals, the OMHA Appeal Number on the adjudicator's decision;
- For Part D appeals requesting expedited review, a statement that you are requesting expedited review;
- The date of the adjudicator's decision (not required for Part D appeals); and
- Your name and signature, and, if applicable, the name and signature of your representative.

Filing by mail:

Mail your appeal and a copy of the enclosed decision to:

Department of Health and Human Services
Departmental Appeals Board
Medicare Appeals Council, MS 6127
Cohen Building Room G-644
330 Independence Ave., S.W.
Washington, D.C. 20201

Filing by fax:

Fax your appeal and a copy of the enclosed decision to **(202) 565-0227**.

Filing by computer:

Using your web browser, visit the Medicare Operations Division Electronic Filing System (MOD E-File) website at <https://dab.efile.hhs.gov/mod>.

To file a new appeal using MOD E-File, you will need to register by:

- (1) Clicking **Register** on the MOD E-File home page;
- (2) Entering the information requested on the "Register New Account" form; and
- (3) Clicking **Register Account** at the bottom of the form.

You will use the email address and password you provided during registration to access MOD E-File at <https://dab.efile.hhs.gov/mod/users/new>. You will be able to use MOD E-File to file and access the specific materials for appeals to which you are a party or a party's representative. You may check the status of any appeal on the website homepage without registering.

Once registered, you may file your appeal by:

- (1) Logging into MOD E-File;
- (2) Clicking the **File New Appeal** menu button on the top right of the screen;
- (3) Selecting the type of appeal you are filing (Request for Review or Request for Escalation); and
- (4) Entering the requested Appeal Information and uploading the requested Appeal Documents on the "File New Appeal – Medicare Operations Division" form. You are required to provide information and documents marked with an asterisk.

At a minimum, the Medicare Appeals Council requires an appellant to file a signed Request for Review and a copy of the enclosed decision. All documents should be submitted in Portable Document Format (PDF) whenever possible. Any document, including a Request for Review, will be deemed to have been filed on a given day, if it is uploaded to MOD E-File on or before 11:59 p.m. EST of that day.

Currently, the documents that may be filed electronically are the:

- (1) Request for Review;
- (2) Appointment of Representative form (OMB Form 0938-0950);
- (3) Copy of Administrative Law Judge or attorney adjudicator decision;
- (4) Memorandum or brief or other written statement in support of your appeal; and
- (5) Request to Withdraw your appeal

No other documents aside from the five (5) listed categories above may be submitted through MOD E-File.

Filing by oral request (for expedited review only):

Oral requests for expedited review of a Part D decision may be made by telephone to **(866) 365-8204**. You must provide the information listed in the bullet points above and a statement that you are requesting an expedited review within 60 calendar days after receipt of this notice of

decision. The Medicare Appeals Council will document the oral request in writing and maintain the documentation in the case file.

Please note that your request for review will only be expedited if (1) the appeal involves an issue specified in 42 C.F.R. § 423.566(b), but does not include solely a request for payment of a Part D drug that has already been furnished, and (2) the prescribing physician (or other prescriber) indicates, or the Medicare Appeals Council determines, that the standard time frame may seriously jeopardize your life, health, or ability to regain maximum function.

How will the Medicare Appeals Council respond to my appeal?

The Medicare Appeals Council will limit its review to the issues raised in the appeal, unless the appeal is filed by an unrepresented beneficiary/enrollee. It may change the parts of the decision that you agree with. It may adopt, modify, or reverse the decision, in whole or in part, or it may send the case back to OMHA for further action. It may also dismiss your appeal.

Questions?

You may call or write our office. A toll-free phone number and mailing address are at the top of this notice.

Additional information about filing an appeal with the Medicare Appeals Council is available at <http://www.hhs.gov/dab/>. You can also call the Medicare Appeals Council's staff in the Medicare Operations Division of the Departmental Appeals Board at (202) 565-0100 or (866) 365-8204 (toll free), if you have questions about filing an appeal.

cc:

DEBRA M PARRISH
788 WASHINGTON RD
PITTSBURGH, PA 15228

C2C Innovative Solutions, Inc.
DME QIC Appeals—ALJ
P.O. Box 44006
Jacksonville, FL 32231-4006

NOVOCURE INC.
195 Commerce Way
Portsmouth, NH 03801

MAXIMUS
DME QIC Appeals—ALJ
3750 Monroe Avenue
Pittsford, NY 14534-1302

Enclosures:

OMHA-152, Decision
DAB-101, Request for Review

If you have additional evidence, submit it with this request for review. If you need more time, you must request an extension of time in writing now, explaining why you are unable to submit the evidence or legal argument now.

If you are a provider, supplier, or a beneficiary represented by a provider or supplier, and your case was reconsidered by a Qualified Independent Contractor (QIC), the Medicare Appeals Council will not consider new evidence related to issues the QIC has already considered unless you show that you have a good reason for submitting it for the first time to the Medicare Appeals Council.

IMPORTANT: Include the HICN and ALJ Appeal Number on any letter or other material you submit.

This request must be received within 60 calendar days after you receive the ALJ's decision or dismissal, unless we extend the time limit for good cause. We assume you received the decision or dismissal 5 calendar days after it was issued, unless you show you received it later. If this request will not be received within 65 calendar days from the date on the decision or dismissal order, please explain why on a separate sheet.

You must file your request for review in writing with the Medicare Appeals Council at:

Department of Health and Human Services
Departmental Appeals Board
Medicare Appeals Council, MS 6127
Cohen Building Room G-644
330 Independence Ave., S.W.
Washington, D.C. 20201

You may send the request for review by U.S. Mail, a common carrier such as FedEx, or by fax to (202) 565-0227. If you send a fax, please do not also mail a copy. **You must send a copy of your appeal to the other parties and indicate that all parties, to include all beneficiaries, have been copied on the request for review. For claims involving multiple beneficiaries, you may submit a copy of the cover letters issued or a spreadsheet of the beneficiaries and addresses who received a copy of the request for review.**

If you have any questions about your request for review or wish to request expedited review of a claim involving authorization of your prescription drug under Medicare Part D, you may call the Medicare Appeals Council's staff in the Medicare Operations Division of the Departmental Appeals Board at (202) 565-0100. You may also visit our web site at www.hhs.gov/dab for additional information on how to file your request for review.

PRIVACY ACT STATEMENT

The collection of information on this form is authorized by the Social Security Act (section 205(a) of title II, section 702 of title VII, section 1155 of Title XI, and sections 1852(g)(5), 1869(b)(1), 1871, 1872, and 1876(c)(5)(B) of title XVIII, as appropriate). The information provided will be used to further document your claim. Information requested on this form is voluntary, but failure to provide all or any part of the requested information may affect the determination of your claim. Information you furnish on this form may be disclosed by the Department of Health and Human Services or the Social Security Administration to another person or governmental agency only with respect to programs under the Social Security Act and to comply with Federal laws requiring the disclosure of information or the exchange of information between the Department of Health and Human Services, the Social Security Administration, or other agencies.

REQUEST FOR REVIEW OF ADMINISTRATIVE LAW JUDGE (ALJ) MEDICARE DECISION / DISMISSAL

| | |
|--------------------------------------------|-----------------------------------------------------|
| 1. APPELLANT (the party requesting review) | 2. ALJ APPEAL NUMBER (on the decision or dismissal) |
| 3. BENEFICIARY* | 4. HEALTH INSURANCE CLAIM NUMBER (HICN)* |

*If the request involves multiple claims or multiple beneficiaries, attach a list of beneficiaries, HICNs, or other information to identify all claims being appealed.

| | |
|----------------------------------------|-----------------------------------|
| 5. PROVIDER, PRACTITIONER, OR SUPPLIER | 6. SPECIFIC ITEM(S) OR SERVICE(S) |
|----------------------------------------|-----------------------------------|

7. Medicare claim type: ☐ Part A ☐ Part B ☐ Part C - Medicare Advantage
☐ Part D - Medicare Prescription Drug Plan ☐ Entitlement/enrollment for Part A or Part B

8. Does this request involve authorization for an item or service that has not yet been furnished?

☐ Yes If Yes, skip to Block 8.
☐ No If No, Specific Dates of Service:

9. If the request involves authorization for a prescription drug under Medicare Part D, would application of the standard appellate timeframe seriously jeopardize the beneficiary's life, health, or ability to regain maximum function (as documented by a physician) such that expedited review is appropriate? ☐ Yes - ☐ No

I request that the Medicare Appeals Council review the ALJ's ☐ decision or ☐ dismissal order [check one] dated _____. I disagree with the ALJ's action because (specify the parts of the ALJ's decision or dismissal you disagree with and why you think the ALJ was wrong):

(Attach additional sheets if you need more space)

PLEASE ATTACH A COPY OF THE ALJ DECISION OR DISMISSAL ORDER YOU ARE APPEALING.

| | | | | | |
|-----------------------------------------------------|------------|--------|-----------------------------------------------------------------------------------|------------|--------|
| DATE | | | DATE | | |
| APPELLANT'S SIGNATURE (the party requesting review) | | | REPRESENTATIVE'S SIGNATURE (include signed appointment if not already submitted.) | | |
| PRINT NAME | | | PRINT NAME | | |
| ADDRESS | | | ADDRESS | | |
| CITY, STATE, ZIP CODE | | | CITY, STATE, ZIP CODE | | |
| TELEPHONE NUMBER | FAX NUMBER | E-MAIL | TELEPHONE NUMBER | FAX NUMBER | E-MAIL |

(SEE FURTHER INSTRUCTIONS ON PAGE 2)



Department of Health and Human Services
OFFICE OF MEDICARE HEARINGS AND APPEALS
Cleveland, Ohio

Appeal of: **D. CHRISTENSON**

OMHA Appeal No.: **1-8630709341**

Beneficiary: **D. CHRISTENSON**

Medicare: **Part B**

Medicare No.: *******3639A**

Before: **Scott Watson**
Administrative Law Judge

EXHIBIT LIST

| EXHIBIT NUMBER | DESCRIPTION | PAGE NUMBERS |
|---------------------------|---------------------------------------------------------------------------------------------------------------------------------|-------------------------|
| 1 | Initial, Redetermination and Reconsideration Procedural Documents, Articles and literature, Redacted ALJ decisions | 1-3145 |
| 2 | Medical Records/Evidence Received by CMS Contractors | 1-23 |
| 3 | Request for ALJ Hearing / Appointment of representative form (Beneficiary) 6/17/19 Request for ALJ hearing (Novocure) 7/1/19 | 1-12 |
| 4 | OMHA Proceedings Notice of hearing 7/1/19 Response to NOH 7/5/19 | 1-10 |
| 5 | Pre-Hearing Brief (Beneficiary Rep) 7/8/19 | 1-47 |

Dated: August 12, 2019

¹ Some materials in the exhibited record are dual sided. References to the second side include a notation of (reverse). For example, "Ex. 1, p. 1 (reverse)." The second side of a dual sided page is not included in the page count for the page number range.



Department of Health and Human Services
Office of the Secretary

OFFICE OF MEDICARE HEARINGS AND APPEALS

Cleveland Field Office
200 Public Square, Suite 1300
Cleveland, OH 44114-2316
216-615-4000 (Main)
216-615-7546 (ALJ Watson Team)
216-615-6735 (FAX)
866-236-5089 (Toll Free)

August 12, 2019

DEBRA M PARRISH
788 WASHINGTON RD
PITTSBURGH, PA 15228

Re: ALJ Appeal Number: 1-8630709341
Hearing: Wednesday, August 28, 2019 at 11:00 AM Eastern Time

Notice of Exhibit List for Hearing

Attached is a copy of the exhibit list for the hearing on the above referenced case. This exhibit list updates any list previously sent. The exhibit list identifies what documents we currently have in the case file for your appeal that the Administrative Law Judge will consider. These documents will be made part of the record absent any objections. There may be additional documentation that is pending a determination by the Administrative Law Judge whether the documentation will be considered, such as new evidence submitted for the first time by a provider or supplier, or beneficiary represented by a provider or supplier.

If you have any questions or concerns, please contact the Administrative Law Judge's staff at the team phone number above.

Enclosure: Exhibit List

Cc:
NOVOCURE INC.
195 Commerce Way
Portsmouth, NH 03801

EXHIBIT 5

PARRISH LAW OFFICES

788 WASHINGTON ROAD
PITTSBURGH, PENNSYLVANIA 15228-2021
www.dparrishlaw.com

July 5, 2019

412.561.6250
FAX 412.561.6253
E-mail: info@dparrishlaw.com

VIA PRIORITY MAIL

Judge Scott Watson
Office of Medicare Hearings and Appeals
Cleveland Field Office
200 Public Sq., Suite 1300
Cleveland, OH 44114-2316

JA RECEIVED

JUL - 8 2019

HMMA FILE

RE: Prehearing Brief
ALJ Appeal Nos. 1-8630709341
Appellant/Beneficiary: D. Christenson
Service: E0766
Dates of Services: 11/3/18, 12/3/18, 1/3/19
Hearing Date: Aug. 28, 2019
Our Ref. No.: 19-296

Dear Judge Watson:

Pease find attached a prehearing brief to aid in your analysis.

If you have any questions regarding the foregoing, please do not hesitate to contact me at (412) 561-6250. We appreciate your consideration.

Respectfully submitted,



Debra M. Parrish
Attorney for D. Christenson

Enclosures:

Prehearing Brief with Attachments

cc: Mr. D. Christenson

A. Background

Mr. David Christenson, a 65-year-old husband, father of two, grandfather of two, retired software developer, and Medicare beneficiary, was diagnosed with a glioblastoma in July 2015. His clinician prescribed chemotherapy, radiation, and surgery to treat his glioblastoma (GBM). Mr. Christenson's cancer showed evidence of enhancement in early 2016. Thereafter, Mr. Christenson started using the Optune device to treat his GBM. From that time through the dates of service at issue, Mr. Christenson has had stable MRIs. The supplier submitted claims for the Optune system to the relevant Durable Medical Equipment Contractor (DME MAC) which denied the claims.

The QIC denied the claims asserting "the medical documentation of the efficacy of this device is not within the usual scope and breadth of current medical literature with peer acknowledgement and review." The QIC also asserted that the studies were "not non-biased" because they were supported by Novocure, and there were few clinical trials. Finally, the QIC asserted that although an LCD reconsideration request had been deemed valid, LCD L34823 has not been revised and is still in effect. As described more fully below, the denial is inconsistent with Medicare coverage criteria and the record.

1. Glioblastoma Multiforme (GBM)

Glioblastoma is the most common form of primary brain cancer, but is still very rare (~10,000 cases annually in the U.S.). The National Institutes of Health (NIH) designate glioblastoma multiforme as a rare disease, with few treatment options. See e.g., <https://rarediseases.info.nih.gov/diseases/2491/glioblastoma>. GBM tumors are typically highly aggressive. Survival at initial presentation is approximately 10 months, and upon recurrence, approximately 6 months, even with aggressive chemotherapy.¹ Because it is extremely rare for glioblastoma to metastasize, it is efficient to treat the disease with regional therapy as part of the treatment strategy.

2. Optune (formerly NovoTTF-100A System)

Optune, previously known as the NovoTTF-100A System, is durable medical equipment that delivers alternating electric fields or Tumor Treating Fields to the brain. The device consists of an electric field generator which is connected to four insulated transducer arrays. The arrays are placed on the patient's scalp and deliver the Tumor Treating Fields Therapy ("TTFT") to the patient's glioblastoma. Basically, the fields slow the replication of the cancer cells or stop their growth all together. The fields may also destroy some of the cancer cells.

¹ Rulseh et al. "Long-term survival of patients suffering from glioblastoma multiforme treated with tumor-treating fields." World Journal of Surgical Oncology at 1 (2012).

Optune is FDA-approved for recurrent and newly diagnosed glioblastoma multiforme (GBM) brain tumors. On January 1, 2014, CMS classified the Optune device as DME requiring frequent and substantial servicing, which is billed under HCPCS code E0766 as a monthly rental through the duration of medical necessity. Optune has been shown to extend the lives of patients suffering from glioblastoma tumors.

B. Literature/Professional Societies

Optune is the subject of numerous peer-reviewed published studies that demonstrate the safety and efficacy of the Optune system and TTFT generally. The studies are reported in some of the most prestigious journals in our country including JAMA (the Journal of the American Medical Association). See submitted studies. Optune is included in the National Comprehensive Cancer Network (NCCN) guidelines for recurrent glioblastoma and for newly diagnosed GBM in combination with temozolomide. See submitted guidelines. The studies concluded the following:

- The final analysis of the randomized phase 3 trial (695 patients) found that the addition of Optune to standard chemotherapy treatment "resulted in statistically significant improvement in progression-free survival and overall survival" over patients that were treated with chemotherapy alone. Stupp et al. at 2315 (JAMA 2017). See also, interim analysis of 315 patients from this study (adding Optune to maintenance chemotherapy "significantly prolonged progression-free and overall survival"). Stupp et al. at 2542 (JAMA 2015).
- These important results come after a ten-year period of more than 23 randomized trials of new treatment modalities or products for glioblastoma that all "failed to demonstrate improved survival." JAMA 2017 at 2314-2315.
- Remarkably, adding Optune to traditional chemotherapy treatment "resulted in statistically significant longer deterioration-free survival in global health status, physical and emotional functioning, pain, and weakness of legs." Taphoorn et al. at E7 (JAMA Oncology 2018).
- As far back as 2012, researchers reported that in a study of 237 patients that received either Optune treatment or chemotherapy that the treatment was at least as effective as chemotherapy alone in terms of median survival, without the toxicity risks. Stupp et al. at 8-9 (European J of Cancer 2012).

To the extent the QIC denied the claim based on the lack of quantification of effectiveness of the device generally, the peer-reviewed literature shows the opposite. Indeed, the Data Safety Monitoring Board for the clinical trial for newly diagnosed glioblastoma (*and patients that suffered recurrences during the trial*) found the data so compelling, they recommended early termination and allowing patients who were not receiving the treatment to be

able to cross over and receive the treatment, deeming it unethical to withhold it. The FDA agreed. The outcomes data from this trial represents results for both newly diagnosed patients and those that suffered recurrences during the trial. Please see the attached bibliography regarding TTFT which shows numerous peer-reviewed articles published on TTFT and its clinical application. Contrast the foregoing with the exhibit list reflecting that the DMAC has not considered any of the literature or evidence that has been published in the past four years. In either event, on May 28, 2019, the Civil Remedies Division ruled the LCD record did not support the validity of the LCD under the reasonableness standard. On May 9, 2019, the DMACs issued a draft LCD extending Medicare coverage to TTFT.

A. The QIC's assertions regarding peer-acknowledgement is belied by the evidence.

The QIC asserted, "The medical documentation in support of efficacy is not within the usual scope and breadth of current medical literature with peer acknowledgement and review." Respectfully, the sentence and logic are difficult to follow. In terms of the breadth and scope of the peer-reviewed literature, a PubMed search reveals over 100 peer-reviewed articles ranging from randomized controlled trials, to case reports, to meta-analyses. The scope and breadth are particularly remarkable given the orphan status of the disease. In the past 10 years, TTFT was the only positive clinical trial and breakthrough treatment in glioblastoma. The pivotal studies were published in the Journal of the American Medical Association (JAMA), one of the most prestigious journals in the United States and one of the most cited journals in the world. Certainly, in view of the number of publications and the prestigious peer-reviewed articles that exist, it is difficult to understand the QIC's assertion that the studies do not have peer acknowledgement and review. Further, the peer-reviewed literature was and is so strong, that TTFT enjoys a level one recommendation in the NCCN guidelines for newly diagnosed glioblastoma. A cursory review of the NCCN guidelines reflects that less than ten percent of cancer treatments enjoy such "acknowledgement." Finally, based on the strength of the outcomes seen, the Data Safety Monitoring Board (DSMB) recommended early termination of the clinical trial so that those in the control arm of the clinical trial could cross over and receive treatment. This was so because it would have been unethical to withhold this life-saving treatment from the control group. Thus, the effectiveness of the treatment certainly enjoyed the "acknowledgement and review" of the DSMB and the FDA.

B. The QIC's assertions regarding the clinical trials are belied by the evidence.

The QIC asserted, "More specifically, the QIC has reviewed the peer reviewed and evidence based literature relative to clinical trials for TTFT, and has found the literature and clinical trials to be limited in number and the clinicals trial not non-biased; that is, the clinical trials were not independent, but funded by Novocure." Respectfully, the sentence and logic are difficult to follow. As noted above, GBM is an orphan disease with a difficult prognosis. More than one randomized controlled clinical trial was performed and reported in the peer-reviewed literature and more than 50 articles regarding TTFT for glioblastoma have been reported in the peer-reviewed literature. One of the seminal clinical trials resulted in multiple publications in

the Journal of the American Medical Association, one of the most prestigious journals in the United States. On March 6, 2019, the Contractor Advisory Committee (CAC) recommended Medicare coverage of TTFT.² The experts found that the peer-reviewed literature shows the treatment is safe and effective. The experts did not find that the studies were limited in number or biased.

With respect to the “not non-biased” assertion, it is unclear if the QIC is attempting to assert that the manufacturer’s funding of the clinical trials resulted in biased publications that could not support Medicare coverage. The studies were conducted at some of the most prestigious academic institutions in the United States by academic researchers. Most of the published clinical research on a medical intervention is sponsored in the United States. Indeed, Medicare often requires industry to sponsor certain studies as a condition of Medicare coverage. A cursory review of the literature supporting most LCDs shows that they are industry-sponsored studies. Industry sponsorship does not make a peer-reviewed study, written by academic authors, “not non-biased” such that the study cannot support Medicare coverage. If such a standard applied, Medicare would be precluded from considering most of the peer-reviewed literature published with respect to a technological advancement – an absurd result.

With respect to the number of clinical trials, Appellant notes that GBM is an orphan disease with a high mortality rate. Because the treatment is so effective, the FDA deemed it unethical to continue a study that withheld such an effective treatment from those battling a fatal disease. This is consistent with the Declaration of Helsinki, paragraph 18.³ The CAC recognized that just as the FDA deemed it unethical to continue the clinical trial, it would be unethical to even begin more clinical studies which involved withholding a proven effective treatment for a fatal disease. A “limited number” of clinical trials is common when a treatment is proven so effective for a fatal condition. After the first study determining that a tourniquet is an effective treatment to prevent people from dying from arterial bleeding, ethically, a second study cannot be conducted. Likewise, with TTFT, given the conclusive effectiveness, additional trials that withhold the treatment cannot be conducted ethically.

C. Widespread Adoption

Based on the strength of the peer-reviewed literature and the lack of medical alternatives,

² See <https://med.noridianmedicare.com/web/jddme/policies/lcd/contractor-advisory-committee>.

³ See World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects: “When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.” The Declaration of Helsinki finds its roots in the Nuremberg Code which required informed consent for human clinical trials after the horrific experiments conducted in concentration camps during WWII. The quoted section has been interpreted to preclude continuation of a clinical trial when effectiveness has been established for a fatal illness.

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July 5, 2019

the Optune system has been certified at more than 800 cancer treatment centers, and has been prescribed by over 1100 physicians in 50 states, the District of Columbia, and Puerto Rico, for over 7200 patients. Virtually every major payor in the United States covers the Optune system for individuals diagnosed with a glioblastoma. These payors include, among others, Highmark, Aetna, Anthem, Humana, Kaiser, UnitedHealthcare, Cigna, Harvard Pilgrim, Geisinger, HealthPartners, and several Blue Cross plans. TTFT is used in 59 of the 62 NCI-designated cancer centers.

Indeed, support for the effectiveness and widespread adoption of the TTFT device is illustrated in CMS' assignment of a HCPCS code to the technology. When an existing HCPCS code does not adequately describe a device, a supplier applies to the HCPCS workgroup for a new HCPCS code. The code communicates relevant coverage decisions and criteria, fee schedule amounts, and billing information. In view of the criteria required to get a new HCPCS code, it is difficult for a DME device to obtain a HCPCS code. A review of the 2016-2017 DMEPOS HCPCS application summary documents reflects that only five new HCPCS codes were established although there were 63 new-code requests.⁴

For the HCPCS workgroup to award a HCPCS code for a device, CMS must have information that shows the technology (a) is deemed safe and effective by the FDA, (b) clinical studies demonstrate its use results in a significantly improved medical outcome or a significantly superior clinical outcome, (c) it is significantly functionally or therapeutically different from already-coded DME, and (d) has achieved sufficient adoption by the relevant medical community to justify the "administrative burden" of adding a new HCPCS code. See HCPCS Decision Tree attached to the reconsideration request. Thus, CMS considers coverage criteria when awarding a HCPCS code.⁵

D. The LCD

LCD L34823 does not reflect consideration of the required elements or provide a rationale. An LCD that on its face fails to conform to the requirements of the Medicare Program Integrity Manual, Ch. 13, is not entitled to deference. Accordingly, LCD L34823 should not be applied. As noted above, the Civil Remedies Division found the LCD record did not support the validity of the LCD under the reasonableness standard.

In view of the LCD's obvious failure to reflect the peer-reviewed literature, consensus of experts, and acceptance by the relevant medical community (mandatory considerations for a valid LCD), the LCD should not be used to preclude Medicare coverage of a device that meets Medicare's coverage criteria and which is reasonable and medically necessary to treat Mr.

⁴ Revision requests were not included in the total number of code applications. June 7, 2017 and June 8, 2017 DMEPOS HCPCS Application Summaries available at:

<https://www.cms.gov/Medicare/Coding/MedHCPCSGenInfo/HCPCS-Application-Summaries.html>.

⁵ See www.ncbi.nlm.gov/PMC/articles/PMC3865619 for an article "HCPCS Coding: An Integral Part of Your Reimbursement Strategy" by Marcia Nusgart.

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Christenson's GBM.

Notably, Administrative Law Judges are not bound by LCDs. 42 C.F.R. § 405.1062. Given the beneficiary's limited treatment options and the rarity of the disease, in addition to the compelling support for the effectiveness of the device as represented by clinical study outcomes, professional societies' statements and policies, the FDA's approval, and other payors' policies, Appellant believes the LCD should not be deferred to for Mr. Christenson's claims.

E. Collateral Estoppel

Mr. Christenson previously litigated the issue of coverage of his TTFT treatment and coverage was ordered. That is, after a full and fair opportunity to litigate the issue, coverage was ordered finding the TTFT was safe and effective and medically reasonable and necessary for Mr. Christenson - twice. The Secretary chose not to appeal those decisions and they have become final. The Secretary is barred by the doctrine of collateral estoppel/issue preclusion from re-litigating those issues with respect to Mr. Christenson. As noted by a unanimous Supreme Court:

We have long favored application of the common-law doctrines of collateral estoppel (as to issues) and res judicata (as to claims) to those determinations of administrative bodies that have attained finality. When an administrative agency is acting in a judicial capacity and resolves dispute issues of fact properly before it which the parties have had an adequate opportunity to litigate, the courts have not hesitated to apply res judicata to enforce repose. Such repose is justified on the sound and obvious principle of judicial policy that a losing litigant deserves no rematch after a defeat fairly suffered, in adversarial proceedings, on an issue identical in substance to the one he subsequently seeks to raise. To hold otherwise would, as a general matter, impose unjustifiably upon those who have already shouldered their burdens, and drain the resources of an adjudicatory system with disputes resisting resolution. The principle holds true when a court has resolved an issue, and should do so equally when the issue has been decided by an administrative agency, be it state or federal, which acts in a judicial capacity.

See Astoria Federal Savings and Loan Assoc. v. Solimino, 501 U.S. 104, 107-8 (1991) (internal citations and quotations omitted). The application of issue preclusion would not work as basic unfairness against the Secretary and there are no special circumstances that would make it unfair to apply the doctrine. As a result, the Secretary is barred by collateral estoppel from re-litigating those issues with respect to Mr. Christenson and coverage should be ordered.

F. Reimbursement Amount

PREHEARING BRIEF - JUDGE SCOTT WATSON
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DOS: 11/3/2018 through 1/3/2019
HEARING DATE: Aug. 28, 2019
July 5, 2019

If Medicare coverage is found, payment for DME is made under a regulation, 42 C.F.R. §414.210(a), which states that:

... Medicare pays for [DME] ... on the basis of 80 percent of the lesser of:

- (1) the actual charge for the item; [or]*
- (2) the fee schedule amount for the item, as determined in accordance with §§414.220 through 414.232.*

Because no fee schedule exists, payment is 80% of the amount billed. See also Medicare Appeal Council Decision for ALJ 1-178898474.

G. Conclusion

This is the technology that clinicians treating central nervous system tumors have embraced. No basis exists to deny Medicare coverage of a device that is shown in the peer-reviewed literature to be a safe and effective treatment for glioblastoma, a life-threatening condition. The Optune system was approved as safe and effective by the FDA. The peer-reviewed literature further supports its efficacy and the improved clinical outcome of patients who use the device. It is incorporated in the NCCN guidelines (considered the gold standard for cancer care), and it enjoys widespread adoption by clinicians and all the major payors in the United States based on the foregoing. The Medicare beneficiary has no reasonable medical alternatives. Mr. Christenson's survival has exceeded the average time periods outlined above, if the QIC insists on a "quantification" of the effects of the device. The claims should be approved.

Attachments:

- A: May 28, 2019 CRD Order
- B: May 9, 2019 draft LCD
- C: Prior ALJ Decisions

ATTACHMENT A:

**May 28, 2019 CRD Order
(C-19-396)**

Department of Health and Human Services

DEPARTMENTAL APPEALS BOARD

Civil Remedies Division

In re LCD Complaint:
Tumor Treatment Field Therapy
LCD ID Number: L34823
Contractor: CGS Administrators, LLC

Docket No. C-19-396

Date: May 28, 2019

**ORDER REGARDING DISCOVERY AND
ADDITIONAL EVIDENCE**

On May 20, 2019, CGS Administrators, LLC (CGS) filed its "Contractor's Response to the Aggrieved Party's Statement Regarding the LCD Record, Motion to Strike the LCD as Invalid, and Motion to Supplement Complaint (CGS response). Under the regulations, the next step is for me to evaluate the evidence that has been submitted and determine if "the LCD record is complete and adequate to support the validity of the LCD" under the reasonableness standard. 42 C.F.R. § 426.425(c)(1). For the reasons stated below, I conclude that the record presently is insufficient to support the validity of the challenged provision in LCD L34823. As a result, I order the parties to indicate whether they want me to close the record in this case or whether they want to engage in discovery or otherwise provide me with additional evidence. 42 C.F.R. § 426.425(c)(3).

I. The LCD's record does not support the LCD's validity.

After I accepted the Aggrieved Party's Complaint in this matter, in conformance with the regulations governing this case, I ordered CGS to file the LCD record, the Aggrieved Party to file a statement explaining why the LCD is not valid, and CGS to file a response defending the LCD. See 42 C.F.R. §§ 426.410(d)(3), 426.425(a)-(b). The parties have completed their submissions. I have reviewed the submissions and conclude that the LCD record is insufficient to support the LCD's categorical denial of coverage for tumor treatment field therapy (E0766) (TTFT).

A. The Aggrieved Party has standing to challenge the LCD.

CGS indicated that the Aggrieved Party's "LCD complaint is inapplicable as binding to the [Medicare Advantage] Plan" because Medicare Advantage Plans "have the option of providing individualized care if desired . . . and thus, are not bound to cover only Medicare-covered services." CGS Response at 1. Although not entirely clear, CGS appears to be challenging the Aggrieved Party's standing to challenge the LCD.

If this is the case, CGS is mistaken in its argument because an "Aggrieved party" includes enrollees in Medicare managed care plans so long as coverage for a service was denied based on the challenged LCD. 42 C.F.R. § 426.110. The Aggrieved Party meets these requirements. A. Ex. 8 at 5-6. Therefore, the Aggrieved Party has standing to challenge the LCD. 42 C.F.R. § 426.320(a).

B. An Aggrieved Party may challenge an LCD because it is outdated.

CGS asserted that the LCD record shows that the LCD was valid at the time the LCD was adopted. CGS further indicated that there is a reconsideration process for revising LCDs in the Medicare Program Integrity Manual, Chapter 13. CGS then concluded that "[n]either the relevant Statutes, Federal rules and regulations, nor sub-regulatory guidance issued by [the Centers for Medicare & Medicaid Services (CMS)] contemplated the role of an LCD Challenge as an alternate pathway for an LCD Reconsideration." CGS Response at 3-4, 7.

CGS misunderstands both the LCD challenge process and how it relates to the LCD reconsideration process. Congress established LCDs and provided some basic requirements related to the development of LCDs. 42 U.S.C. § 1862(l)(5). However, Congress also established an LCD review process, to be conducted by an administrative law judge (ALJ). 42 U.S.C. § 1395ff(f)(2). This process is meant to determine the validity of the LCD. *Id.* § 1395ff(f)(2)(i)(I). In promulgating the regulations to implement this process to challenge an LCD, the Secretary of Health and Human Services (Secretary) made it clear that the process for challenging the validity of an LCD may be invoked because "a challenger may believe that a policy that was correct when it was issued has become outdated and is no longer valid in light of advances in medicine." 68 Fed. Reg. 63,692, 63,700 (Nov. 7, 2003). In fact, the Secretary expressly permitted aggrieved parties to submit new evidence concerning the LCD so that the ongoing validity of the LCD could be tested. *Id.*; *see also* 42 C.F.R. § 426.403.

Further, the Secretary was fully aware of the LCD reconsideration process and provided procedures by which the contractor or the ALJ could evaluate whether new evidence submitted in the case warranted a reconsideration of the LCD. 42 C.F.R. §§ 426.340, 426.417. As stated in the preamble to the final rule:

We have modified the procedures at § 426.340 to allow the ALJ/Board to make a preliminary determination on whether the new evidence submitted would have a significant bearing on the validity of the LCD/NCD. If the evidence is found significant, it would be sent to the contractor/CMS to determine whether the contractor/CMS agrees that the evidence warrants a formal reconsideration. As mentioned earlier, the reconsideration process would be time limited but would allow the public to submit medical and scientific evidence and allow the agency to fully develop the record in light of advances in medical science. Following the time-limited reconsideration, a supplemental record would be filed and the adjudication could continue, if necessary.

This approach will provide the contractor/CMS the initial opportunity to permit medical and scientific experts to examine the new evidence and to make findings of fact concerning the new evidence. Among other things, the statute requires that the ALJ/Board "shall defer only to the reasonable findings of fact" and it was impossible for the agency to have made findings on evidence that did not yet exist or that had not been furnished to the agency for consideration. We believe this approach is necessary to ensure that the medical and scientific opinions of the agency experts illuminate the record, since these appeals could involve very technical medical and scientific material related to the new evidence.

68 Fed. Reg. at 63,700. The Secretary knew that the LCD review process and reconsideration processes are different. The preamble to the final rule stated:

5. Differences Between an LCD/NCD Review and an LCD/NCD Reconsideration

The main difference between an LCD/NCD review under section 522 of the BIPA and an LCD/NCD reconsideration is the avenue an individual chooses to take to initiate a change to a coverage policy and who may initiate the review. All interested parties, including an aggrieved party, may request a reconsideration of an LCD or NCD, rather than filing a complaint to initiate the review of an LCD or NCD. Conversely, only an aggrieved party may file a complaint to initiate the review of an LCD or NCD. If the aggrieved party

believes that we, or the contractor, misinterpreted evidence or excluded available evidence in making the coverage determination or has new evidence to submit, then the aggrieved party has the option to file a request for a reconsideration by the contractor or us, respectively, or to file a complaint to seek review by an adjudicator.

In the reconsideration process, all interested parties, not just aggrieved parties, have the opportunity to submit new scientific and medical evidence for review by individuals with medical and scientific expertise. The reconsideration process permits experts to make judgments about those policies, rather than using an adjudicatory proceeding.

68 Fed. Reg. at 63,694. Another major distinction between the LCD review process before an ALJ and the reconsideration process before a contractor is that an ALJ can only decide that an LCD provision is no longer valid, but cannot revise the LCD provision. 42 C.F.R. §§ 426.405(d)(14), 426.450(a)(2).

C. The LCD's record is inadequate to support the validity of the LCD.

CGS filed the record of the LCD in this case. The LCD was published in 2015, and the entire LCD record consists of documentation and reports from that time and earlier. However, the Aggrieved Party has submitted many documents and reports that more recently show the efficacy of TTFT, at least within certain parameters. Significantly, the Aggrieved Party has submitted 21 out of the 29 reports and journal articles that CGS has considered in the reconsideration process that CGS has already started. A. Exs. 5-6, 12, 70-72, 82, 95, 122-123, 125, 129, 136-137, 139, 143, 146, 150, 155, 157, 158; CMS Ex. 43 at 10-13. Further, based on these documents, CGS, along with other Medicare contractors, have proposed to remove the categorical prohibition on coverage of TTFT to permit coverage if specific criteria are met. CMS Ex. 44.

II. The parties may request to engage in discovery and submit additional evidence.

The regulations state:

If the ALJ determines that the LCD record is not complete and adequate to support the validity of the LCD, the ALJ permits discovery and the taking of evidence in accordance with §§426.432 and 426.440 and evaluates the LCD in accordance with §426.431.

42 C.F.R. § 426.425(c)(3).

In the present case, the Aggrieved Party appears likely to have submitted all of the evidence it plans to submit and CGS has already indicated that it neither plans to submit written direct testimony for any witnesses nor cross-examine the Aggrieved Party's witnesses. However, the parties will indicate by **June 5, 2019**, if they want to pursue discovery or to submit additional evidence.

Further, if the parties have objections to any of the exhibits submitted thus far by the other party, written objections must be submitted by **June 5, 2019**.

When the evidentiary record closes in this case, I will next need to determine whether the new evidence in the record is significant and permit CGS an opportunity to conduct a reconsideration. 42 C.F.R. § 426.340.



Scott Anderson
Administrative Law Judge

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ATTACHMENT B:

Proposed LCD for TTFT

Proposed Local Coverage Determination (LCD): Tumor Treatment Field Therapy (TTFT) (DL34823)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Please Note: This is a Proposed policy.

Proposed LCDs are works in progress that are available on the Medicare Coverage Database site for public review.

Proposed LCDs are not necessarily a reflection of the current policies or practices of the contractor.

Contractor Information

| CONTRACTOR NAME | CONTRACT TYPE | CONTRACT NUMBER | JURISDICTION | STATE(S) |
|------------------------------------|---------------|-----------------|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CGS Administrators, LLC | DME MAC | 17013 - DME MAC | J-B | Illinois Indiana Kentucky Michigan Minnesota Ohio Wisconsin |
| CGS Administrators, LLC | DME MAC | 18003 - DME MAC | J-C | Alabama Arkansas Colorado Florida Georgia Louisiana Mississippi North Carolina New Mexico Oklahoma Puerto Rico South Carolina Tennessee Texas Virginia Virgin Islands West Virginia |
| Noridian Healthcare Solutions, LLC | DME MAC | 16013 - DME MAC | J-A | Connecticut District of Columbia Delaware Massachusetts Maryland Maine New Hampshire |

| CONTRACTOR NAME | CONTRACT TYPE | CONTRACT NUMBER | JURISDICTION | STATE(S) |
|------------------------------------|---------------|-----------------|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | | | | New Jersey New York - Entire State Pennsylvania Rhode Island Vermont |
| Noridian Healthcare Solutions, LLC | DME MAC | 19003 - DME MAC | J-D | Alaska American Samoa Arizona California - Entire State Guam Hawaii Iowa Idaho Kansas Missouri - Entire State Montana North Dakota Nebraska Nevada Oregon South Dakota Utah Washington Wyoming Northern Mariana Islands |

Proposed LCD Information

Document Information

Source LCD ID

L34823

Proposed LCD ID

DL34823

Original ICD-9 LCD ID

L34665

L34738

L34730

L34734

Proposed LCD Title

Tumor Treatment Field Therapy (TTFT)

AMA CPT / ADA CDT / AHA NUBC Copyright Statement

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CMS National Coverage Policy

N/A

Coverage Guidance**Coverage Indications, Limitations, and/or Medical Necessity**

For any item to be covered by Medicare, it must 1) be eligible for a defined Medicare benefit category, 2) be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member, and 3) meet all other applicable Medicare statutory and regulatory requirements.

The purpose of a Local Coverage Determination (LCD) is to provide information regarding "reasonable and necessary" criteria based on Social Security Act § 1862(a)(1)(A) provisions.

In addition to the "reasonable and necessary" criteria contained in this LCD there are other payment rules, which are discussed in the following documents, that must also be met prior to Medicare reimbursement:

- The LCD-related Standard Documentation Requirements Article, located at the bottom of this policy under the Related Local Coverage Documents section.
- The LCD-related Policy Article, located at the bottom of this policy under the Related Local Coverage Documents section.
- Refer to the Supplier Manual for additional information on documentation requirements.
- Refer to the DME MAC web sites for additional bulletin articles and other publications related to this LCD.

For the items addressed in this LCD, the "reasonable and necessary" criteria, based on Social Security Act § 62(a)(1)(A) provisions, are defined by the following coverage indications, limitations and/or medical necessity.

INITIAL COVERAGE FOR NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME:

Tumor treatment field therapy (E0766) is only covered for the treatment of newly diagnosed Glioblastoma Multiforme (GBM) when all of the following criteria are met:

1. The beneficiary has histologically confirmed (World Health Organization (WHO) grade IV astrocytoma), newly diagnosed, supratentorial GBM; and,
2. The beneficiary has received initial treatment with maximal debulking surgery, followed by chemotherapy and radiotherapy; and,
3. Tumor treatment field therapy is initiated within 7 weeks from the last dose of concomitant chemotherapy or radiotherapy; and,
4. The beneficiary is receiving care for GBM at a National Cancer Institute-designated Cancer Center, National Cancer Institute-designated Comprehensive Cancer Center, or National Cancer Institute-designated Cancer Research Network facility; and,
5. The beneficiary has no evidence of progression by Response Assessment in Neuro-Oncology (RANO) criteria; and,
6. The beneficiary has a Karnofsky Performance Score (KPS) of at least 70; and,
7. The beneficiary will use TTFT for at least 18 hours/day.

If all of the coverage criteria above are not met, claims for code E0766 will be denied as not reasonable and necessary.

CONTINUED COVERAGE FOR NEWLY DIAGNOSED GBM BEYOND THE FIRST THREE MONTHS OF THERAPY:

Continued coverage of TTFT (E0766) beyond the first three months of therapy requires that no sooner than the 60th day but no later than the 91st day after initiating therapy, the treating practitioner must conduct a clinical re-

evaluation and document that the beneficiary is continuing to use and is benefiting from TTFT.

Documentation of clinical benefit is demonstrated by:

1. Face-to-face clinical re-evaluation by the treating practitioner; and,
2. Objective evidence of adherence to the use of TTFT, reviewed by the treating practitioner.

Adherence to therapy is defined as the use of TTFT for at least 18 hrs/day (see criterion 7 above).

If the above criteria are not met, continued coverage of TTFT will be denied as not reasonable and necessary.

If the practitioner re-evaluation does not occur until after the 91st day but the evaluation demonstrates that the beneficiary is benefiting from TTFT as defined in criteria 1 and 2 above, continued coverage of TTFT will commence with the date of that re-evaluation. See Policy Specific Documentation Requirements in the LCD-related Policy Article, located in the Related Local Coverage Documents section of this LCD, for information about KX modifier use.

RECURRENT GBM

Tumor treatment field therapy (E0766) will be denied as not reasonable and necessary for the treatment of recurrent GBM.

OTHER USES

The use of TTFT for any indications other than newly diagnosed GBM will be denied as not reasonable and necessary.

GENERAL

A Detailed Written Order (DWO) (if applicable) must be received by the supplier before a claim is submitted. If the supplier bills for an item addressed in this policy without first receiving a completed DWO, the claim shall be denied as not reasonable and necessary.

An item/service is correctly coded when it meets all the coding guidelines listed in CMS HCPCS guidelines, LCDs, LCD-related Policy Articles, or DME MAC articles. Claims that do not meet coding guidelines shall be denied as not reasonable and necessary/incorrectly coded.

Proof of delivery (POD) is a Supplier Standard and DMEPOS suppliers are required to maintain POD documentation in their files. Proof of delivery documentation must be made available to the Medicare contractor upon request. All services that do not have appropriate proof of delivery from the supplier shall be denied as not reasonable and necessary.

Summary of Evidence

Support for TTFT in the treatment of newly diagnosed GBM stems from a study by Stupp et al. (2017), also referred to as the EF-14 study. The EF-14 study was a randomized, open-label trial of 695 patients with histologically-

confirmed glioblastoma multiforme (World Health Organization (WHO) grade IV astrocytoma) whose tumor was resected or biopsied and had completed concomitant radiochemotherapy and TTFT. Of the 695 randomized patients, 637 (92%) completed the trial. Median progression-free survival from randomization was 6.7 months in the TTFT-temozolomide group vs 4.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.52-0.76; $P < .001$). Median overall survival was 20.9 months in the TTFT-temozolomide group vs 16.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76; $P < .001$). Systemic adverse events were similar between the two study arms. Mild to moderate skin toxicity underneath the transducer arrays occurred in 52% of patients who received TTFT-temozolomide vs no patients who received temozolomide alone.

The *National Comprehensive Cancer Network* assigns TTFT a Category 1 recommendation as an option for newly diagnosed GBM.

Analysis of Evidence (Rationale for Determination)

Background

Alternating electric fields are produced by a pulse generator and transmitted by ceramic transducers placed on a patient's head. Tumor Treatment Field Therapy (TTFT) uses alternating electric fields to target cancer cells. The electric fields reportedly attract and repel charged proteins during cancer cell division. Cellular proteins, because they are highly polarized, are presumed to be prevented from moving to their correct locations thus disrupting cancer cell division.

Glioblastoma, also known as glioblastoma multiforme (GBM) is an aggressive type of brain cancer. It is rare, with an incidence of 3.21 cases per 100,000 population per year in the US. Tumor Treatment Field Therapy is an additional option to standard surgical, chemotherapy, and radiotherapy treatment modalities for the treatment of newly diagnosed GBM.

NEWLY DIAGNOSED GBM

In October 2015 the FDA expanded the marketing indications for TTFT to include newly diagnosed GBM (see <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100034S013>). In 2018 the DME MACs received a request to cover TTFT for newly diagnosed GBM. The request for coverage of newly diagnosed GBM is the subject of this proposed LCD.

Contractor Advisory Committee (CAC)

Following an independent review of the literature, the DME MACs assembled a 13-member specialty-focused CAC, comprised of a national panel of neuro-oncologists, neurosurgeons and experts in the field of oncologic treatment. The CAC meeting was held on March 6, 2019 in Baltimore, Maryland. Five (5) Key Questions were discussed by the CAC members, and confidence in each Key Question scored (Chair and Industry Representative were excluded from scoring). Confidence was rated on a scale of 1-5, with 1 indicative of low confidence and 5 indicating high confidence.

The following is a summary of the CAC Panel scoring for each Key Question and the related discussion.

- | | | |
|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| 1. | How confident are you that there is sufficient evidence to determine that TTFT for newly diagnosed GBM can provide net positive health outcomes in the Medicare-eligible population? | Scoring Member Average |
|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|

| | |
|----------------------------------------------------------------------|-------------|
| <i>1 Low Confidence — 2 — 3 Intermediate — 4 — 5 High Confidence</i> | 3.82 |
|----------------------------------------------------------------------|-------------|

The members noted that both Progression Free Survival (PFS) and Overall Survival (OS) were both increased in the EF-14 treatment arm, and migrated together, for both Medicare age eligible and non-eligible populations, in spite of the small group of the latter. Comments were made as to what constitutes adequate PFS and OS, and there was acknowledgement that additional months of improved quality of life in a disease such as GBM is a desirable outcome.

Several substantial concerns were raised in regard to net positive health outcomes. Two were related to study design, one to the philosophical approach to assessment of a new technology, and one to concerns related to conflicts of interest. In spite of the relative consensus on the goodness of metrics to reflect positive health outcomes, significant concerns were expressed -- the study design, lack of sham control group and data gaps regarding volume of study subjects, subset analyses and the lack of corroborative additional clinical study. There was also discussion but not consensus as to whether or not the bar should be higher for net positive health outcomes for such a new technology. Additional concerns were related to the lack of clarity regarding clinical mechanism of action and concerns regarding delivery and dose effect, and geographical localization of the treatment field. Concerns related to potential conflict of interest in study funding and analyses were also discussed.

- | | | |
|----|---------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| 2. | How confident are you that the available evidence demonstrates adequate predictors of success in Medicare-eligible population? | Scoring Member Average |
|----|---------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|

| | |
|----------------------------------------------------------------------|-------------|
| <i>1 Low Confidence — 2 — 3 Intermediate — 4 — 5 High Confidence</i> | 3.45 |
|----------------------------------------------------------------------|-------------|

When considering this question, there was repeated discussion of volume and data gaps. The most substantial concern revolved around the smallness of the Medicare age eligible subpopulation. There was consensus that predictors of response in the age eligible Medicare population were sparse.

- | | | |
|----|----------------------------------------------------------------------------------------------------------------|-----------------------------------|
| 3. | How confident are you that TTFT is generally accepted by the medical community for newly diagnosed GBM? | Scoring Member Average |
|----|----------------------------------------------------------------------------------------------------------------|-----------------------------------|

| | |
|----------------------------------------------------------------------|-------------|
| <i>1 Low Confidence — 2 — 3 Intermediate — 4 — 5 High Confidence</i> | 2.91 |
|----------------------------------------------------------------------|-------------|

This question generated the most concerns regarding how the standard of care was established, how the provider community was defined and segmented, and what conflicts may contribute to drive adoption. There was consensus that guidelines are just one factor in the determination as to whether TTF is generally accepted in the medical community.

In balance the group did think that regardless of how practitioners were notified of the availability of TTF for GBM, there was broad superficial penetration in the USA community, but

that its acceptance as standard of care or generally accepted practice was not clear.

- | | | |
|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| 4. | How confident are you that scientific evidence supports mitotic spindle disruption and cellular apoptosis as the mechanism of action of TTFT? | Scoring Member |
| | | Average |

1 Low Confidence — 2 — 3 Intermediate — 4 — 5 High Confidence

3.27

There was discussion here as to the lack of actual human data to demonstrate the mechanism of action, but consensus that there was a plethora of preclinical data did uniformly seem to demonstrate mitotic spindle disruption and apoptosis as a mechanism of action of tumor cell death.

- | | | |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| 5. | How confident are you that there are no significant evidence gaps that may impact positive health outcomes in the Medicare-eligible population? | Scoring Member |
| | | Average |

1 Low Confidence — 2 — 3 Intermediate — 4 — 5 High Confidence

2.91

There was consensus in the group that there remained significant gaps in evidence that the CAC members would like to see explored, either through controlled trials or in a real world evidence study paradigms. There was consensus that more data is needed to identify the place of TTFT in therapy across a more broad range of patient population and within the treatment algorithm for GBM and to further explore its mechanism of action, prognostic features, and predictors of response.

There was discussion of the need to review the evolving evidence rapidly since the standard of care evolves so rapidly in this area. There was consensus that more data is needed to identify the place of TTFT in therapy across a more broad range of patient population and within the treatment algorithm for GBM and to further explore its mechanism of action, prognostic features, and predictors of response. Specific additional areas recommended for study included:

- Dose density and power
- Demographic diversity of subjects
- Prognostic indicators
- Impact on caretakers
- More on quality of life
- Medical economic assessment
- The best sequencing of treatment including where in the algorithm is TTFT best placed
- Exploration of the human mechanism of action

CONCLUSION

The use of TTFT for the treatment of newly diagnosed GBM appears to be gaining acceptance in the neuro-oncology community in the United States. However, there are evidence gaps that preclude unreserved support for the use of TTFT in the treatment of newly diagnosed GBM in Medicare beneficiaries. Thus, the DME MACs are recommending coverage of TTFT only when Medicare beneficiaries are receiving their GBM care at a National Cancer Institute-designated Cancer Center, National Cancer Institute-designated Comprehensive Cancer Center, or National Cancer Institute-designated Cancer Research Network facility, in order to ensure optimal management of Medicare-eligible beneficiaries in a field with rapidly changing treatment armamentariums.

RECURRENT GBM

In April 2011 the Food and Drug Administration (FDA) approved the marketing of the NovoTTF-100A (later rebranded Optune®) for the treatment of recurrent GBM. The current LCD for TTFT was effective in August 2014, following an Open Meeting and solicitation of public comments. The DME MACs determined that, based on the strength and quality of the evidence available at that time, TTFT was not reasonable and necessary for the treatment of GBM.

In 2018 the DME MACs received a request to reconsider the decision on recurrent GBM. The requestor, Novocure, did not submit new evidence in support of revised coverage for recurrent disease. Consequently, pursuant to Chapter 13 the CMS Internet Only Manual 100-08, the DME MACs determined that the request was invalid.

Proposed Process Information

Synopsis of Changes

| CHANGES | FIELDS CHANGED |
|---------|----------------|
| N/A | N/A |

Associated Information

DOCUMENTATION REQUIREMENTS

Section 1833(e) of the Social Security Act precludes payment to any provider of services unless "there has been furnished such information as may be necessary in order to determine the amounts due such provider." It is expected that the beneficiary's medical records will reflect the need for the care provided. The beneficiary's medical records include the physician's office records, hospital records, nursing home records, home health agency records, records from other healthcare professionals and test reports. This documentation must be available upon request.

GENERAL DOCUMENTATION REQUIREMENTS

In order to justify payment for DMEPOS items, suppliers must meet the following requirements:

- Prescription (orders)
- Medical Record Information (including continued need/use if applicable)
- Correct Coding
- Proof of Delivery

Refer to the LCD-related Standard Documentation Requirements article, located at the bottom of this policy under

the Related Local Coverage Documents section for additional information regarding these requirements.

Refer to the Supplier Manual for additional information on documentation requirements.

Refer to the DME MAC web sites for additional bulletin articles and other publications related to this LCD.

POLICY SPECIFIC DOCUMENTATION REQUIREMENTS

Items covered in this LCD have additional policy-specific requirements that must be met prior to Medicare reimbursement.

Refer to the LCD-related Policy article, located at the bottom of this policy under the Related Local Coverage Documents section for additional information.

Appendices

Utilization Guidelines

Refer to Coverage Indications, Limitations and/or Medical Necessity

Sources of Information

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Kim EH, Song HS, Yoo SH, Yoon M. Tumor treating fields inhibit glioblastoma cell migration, invasion and

Open Meetings

| MEETING DATE | MEETING STATE(S) | MEETING INFORMATION |
|--------------|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 06/20/2019 | Maryland | Location: Westin Baltimore Washington International Airport 1110 Old Elkridge Landing Rd Linthicum Heights, MD 21090 Time: 9 AM - 12 PM EDT See DME MAC websites for information |

Contractor Advisory Committee (CAC) Meetings

| MEETING DATE | MEETING STATE(S) | MEETING INFORMATION |
|--------------|------------------|--------------------------------------------------------------------------------------------------------|
| 03/06/2019 | Maryland | Location: Centers for Medicare & Medicaid Services 7500 Security Blvd Baltimore, MD 21244 |

MAC Meeting Information URL(s)

N/A

Proposed LCD Posting Date

05/09/2019

Comment Period Start Date

05/09/2019

Comment Period End Date

06/24/2019

Released to Final LCD Date

Please Note: This is not the LCD Effective Date.

N/A

Reason for Proposed LCD

- Request for Coverage by a Supplier

Proposed Contact

DME MAC Medical Directors
Two Vantage Way
Nashville, TN 37228-1504
Two Vantage Way

Coding Information

Bill Type Codes:

Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type. Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

N/A

Revenue Codes:

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory. Unless specified in the policy, services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

N/A

CPT/HCPCS Codes

Group 1 Paragraph:

The appearance of a code in this section does not necessarily indicate coverage.

ICPCS MODIFIERS:

EY - No physician or other licensed health care provider order for this item or service

GA - Waiver of liability statement issued as required by payer policy, individual case

GZ - Item or service expected to be denied as not reasonable and necessary

KX - Requirements specified in the medical policy have been met

HCPCS CODES:

Group 1 Codes:

| CODE | DESCRIPTION |
|-------|-------------------------------------------------------------------------------------------------------------|
| A4555 | ELECTRODE/TRANSDUCER FOR USE WITH ELECTRICAL STIMULATION DEVICE USED FOR CANCER TREATMENT, REPLACEMENT ONLY |

| CODE | DESCRIPTION |
|-------|---------------------------------------------------------------------------------------------|
| E0766 | ELECTRICAL STIMULATION DEVICE USED FOR CANCER TREATMENT, INCLUDES ALL ACCESSORIES, ANY TYPE |

ICD-10 Codes that Support Medical Necessity

Group 1 Paragraph:

Not specified

Group 1 Codes: N/A

ICD-10 Codes that DO NOT Support Medical Necessity

Group 1 Paragraph:

Not specified

Group 1 Codes: N/A

Additional ICD-10 Information

N/A

Associated Documents

Attachments

A52711 - TTFT Policy Article
(PDF - 233 KB)

Related Local Coverage Documents

Article(s)

A55426 - Standard Documentation Requirements for All Claims Submitted to DME MACs

Related National Coverage Documents

N/A

Keywords

N/A

ATTACHMENT C:

Prior Favorable ALJ Decisions for D. C.



Department of Health and Human Services
OFFICE OF MEDICARE HEARINGS AND APPEALS
Cleveland Field Office
Cleveland, Ohio

| | |
|------------------------------------|-----------------------------------------------------------------|
| Appeal of: D. Christenson | ALJ Appeal No.: 1-8285652321 |
| Beneficiary: D. Christenson | Medicare Part B |
| HICN: *****3639A | Before: Thomas S. Tyler U.S. Administrative Law Judge |

DECISION

After carefully considering the evidence and arguments presented in the record, a **FULLY FAVORABLE** on-the-record decision is entered for the Beneficiary.

Procedural History

Novocure, Inc., the provider, submitted claims to Medicare for tumor treatment field therapy (TTFT), electric stimulation cancer treatment (E0766) it provided to the Beneficiary from January 3, 2018 to April 3, 2018. The claims were denied initially and upon reconsideration. The matter was then forwarded to C2C Solutions, Inc., a qualified independent contractor (QIC), which issued an unfavorable decision on December 27, 2018 and found the provider liable for payment of the non-covered services.

The Office of Medicare Hearings and Appeals (OMHA) received the Appellant's timely filed appeal. The remaining amount in controversy meets the jurisdictional requirements for a hearing before OMHA.

A telephone hearing in this matter was scheduled to be held on March 28, 2019 at 1:30 PM EST in Cleveland, Ohio before the undersigned ALJ. However, because all of the issues have been resolved in the Beneficiary's favor, a hearing was not conducted and a decision on-the-record has been entered pursuant to 42 C.F.R. §405.1000(g). All exhibits were entered into the record as evidence.

Issue

The issue is whether the tumor treatment field therapy (TTFT) provided to the Beneficiary from January 3, 2018 to April 3, 2018 is covered under Medicare Part B.

Findings of Fact

The Beneficiary in this case is a 65 year-old man who was diagnosed with glioblastoma (GBM) in July 2015. Specifically, he had a right occipital brain tumor. He had surgery and was treated with chemotherapy and radiation. Thereafter, his physician prescribed the tumor treatment field therapy (TTFT). The TTFT is durable medical equipment that delivers alternating electric fields or tumor treating fields to the brain. The device consists of an electric field generator which is connected to four insulated transducer arrays. The arrays are placed on the patients scalp and deliver the tumor treating fields therapy in order to interfere with the growth of the patient's glioblastoma tumors. (Exhibit 2; Beneficiary's Pre-hearing Brief).

The physician signed a renewal prescription form for Optune on November 29, 2017. (Exhibit 2, p. 56). NOVO-TTF transducers were delivered to the Beneficiary on January 3, 2018, February 3, 2018, March 3, 2018 and April 3, 2018. (*Id.* at pp. 52-55).

The record contains multiple articles regarding the efficacy of the use of Optune for the treatment of both initially discovered and recurring glioblastoma. (Exhibit 1). The following historic information is identified in the documentation:

In April 2011, the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) approved commercial distribution of the Optune device for treatment of adult patients (22 years of age and older) with histologically-confirmed glioblastoma multiforme (GBM) following histologically- or radiologically- confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. In the pre-market approval letter, CDRH noted the device was intended to be used as a monotherapy, and was intended as an alternative to standard medical therapy for GBM after surgical and radiation options had been exhausted.

In October 2015, the CDRH issued a pre-market approval supplement for Optune. The supplement approved Optune as a treatment for adult patients (22 years of age or older) with histologically-confirmed GBM and Optune with temozolomide for the treatment of adult patients with newly diagnosed, supranentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant chemotherapy.

In 2018, the National Comprehensive Cancer Network (NCCN) Guidelines (version 1.2018; March 20, 2018) were updated to include alternating electric field therapy (TTFT) as an NCCN category I recommendation following post-operative standard brain radiation therapy with concurrent temozolomide. (See CD, file "NCCN_CNS_2018.pdf"). (Exhibit 3).

Peer-reviewed literature suggests that tumor-treating fields, also known as alternating electric fields, disrupt the cell division process in cancerous tumors which may lead to programmed cell death, or apoptosis. Tumor treating fields have shown statistically significant improvement in patient survival and outcomes in GBM brain tumors compared with traditional standards of care alone. (Exh. 2, pp. 49-79; See also, CD, Optune Peer Reviewed Literature; *Hearing Record*).

A large number of health care insurance providers have medical policies in place allowing coverage for Optune for the treatment of glioblastoma multiforme when certain conditions are met. These providers include, but are not limited to AETNA, Highmark, Anthem, Humana, Kaiser, United Healthcare, Cigna, Geisinger, and Blue Cross Blue Shield. (See CD, Optune Medical Policies November 2018; *Hearing Record*).

Legal Framework

I. ALJ Review Authority

A. Jurisdiction

An individual who, or an organization that, is dissatisfied with the reconsideration of an initial determination is entitled to a hearing before the Secretary of the Department of Health and Human Services (HHS), provided there is a sufficient amount in controversy and a request for hearing is filed in a timely manner. Social Security Act (Act) § 1869(b)(1)(A).

In implementing this statutory directive, the Secretary has delegated the authority to administer the nationwide hearings and appeals system for the Medicare program to OMHA. See 70 Fed. Reg. 36386, 36387 (June 23, 2005). The ALJs within OMHA issue the final decisions of the Secretary, except for decisions reviewed by the Medicare Appeals Council. *Id.*

A hearing before an ALJ is only available if the remaining amount in controversy is \$160 or more. See 76 Fed. Reg. 59138 (Sept. 23, 2011) and 42 C.F.R. §405.1006(b)(2). The request for hearing is timely if filed within sixty days from the date the party receives notice of the QIC's reconsideration. See 42 C.F.R. § 405.1014(b)(1).

B. Scope of Review

Under the implementation policy of the Centers for Medicare and Medicaid Services, United States Department of Health and Human Services, all appeal requests stemming from a QIC reconsideration are governed by the Administrative Law Judge Hearing Procedures outlined in 42 C.F.R. §§ 405.1000 – 1018. 70 Fed. Reg. 11425 (March 8, 2005).

The issues before the administrative law judge include all the issues brought out in the initial determination, redetermination, or reconsideration that were not decided entirely in the party's favor. However, if evidence presented before the hearing causes the administrative law judge to question a favorable portion of the determination, the administrative law judge will notify the parties before the hearing and may consider it an issue at the hearing. 42 C.F.R. § 405.1032(a).

C. Standard of Review

The Office of Medicare Hearings and Appeals is staffed with Administrative Law Judges who conduct de novo hearings. 42 C.F.R. § 405.1000(d).

II. Principles of Law

A. Statutes and Regulations

The Medicare program, Title XVIII of the Social Security Act (the Act), is administered through the Centers for Medicare and Medicaid Services (CMS), a component of the United States Department of Health and Human Services (HHS). Under the authority of Section 1842(a)(1)(A) of the Act, the Secretary of HHS is authorized to enter into contracts with private entities for the day-to-day operations of the program.

Part B of Title XVIII, the Supplementary Medical Insurance program, provides coverage for a variety of medical services and supplies furnished by physicians, or by others in connection with physicians' services, for outpatient hospital services, and for a number of other specific health-related items and services. Individuals participate voluntarily in the Medicare Part B program and pay a monthly premium.

Sections 1832(a)(2)(B), 1861(s)(6), and 1862(a)(1)(A) of the Act provide that Part B covers durable medical equipment (DME) that is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.

Title XVIII, § 1833(e) of the Act provides that no payment shall be made to any provider of services or other person under this part unless there has been furnished such information as may be necessary in order to determine the amounts due such provider or other person under this part for the period with respect to which the amounts are being paid or for any prior period.

B. Medicare Manual System

Administrative Law Judges may also give consideration to the manuals and rulings issued by the CMS in determining benefit coverage and eligibility. Although not binding on the Administrative Law Judge, the respective manuals provide guidance in the administration of the Medicare program. (*Shalala v. Guernsey Memorial Hospital*, 514 U.S. 87 (1995)).

Section 1871(a)(2) of the Act provides that no rule, requirement or statement of policy, other than a National Coverage Determination ("NCD"), can establish or change a substantive legal standard governing the scope of benefits or payment for services under the Medicare program unless it is promulgated as a regulation by CMS. However, although not subject to the force and effect of the law, CMS and its contractors, have issued policy and guidelines, including Local Coverage Determinations (LCD's) that describe criteria for coverage for selected types of medical services and supplies. NCDs promulgated by the Secretary of HHS under the authority of § 1862(a)(1) of the Act dictate the criteria under which specified services, procedures or supplies are covered by Medicare. NCDs are binding upon ALJs. 42 CFR §405.732(a)(4). "An ALJ may not disregard, set aside or otherwise review an NCD." (42 CFR §405.732(b)(1)).

There is no NCD specific to tumor treatment field therapy. However, there is a local coverage determination that can be found at L34823. Local Coverage Determination, L34823 addresses tumor treatment field therapy (TTFT). It states:

For any item to be covered by Medicare, it must 1) be eligible for a defined Medicare benefit category, 2) be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member, and 3) meet all other applicable Medicare statutory and regulatory requirements. For the items addressed in this local coverage determination, the criteria for "reasonable and necessary", based on Social Security Act § 1862(a)(1)(A) provisions, are defined by the following coverage indications, limitations and/or medical necessity.

For an item to be covered by Medicare, a detailed written order (DWO) must be received by the supplier before a claim is submitted. If the supplier bills for an item addressed in this policy without first receiving the completed DWO, the item will be denied as not reasonable and necessary.

Tumor treatment field therapy (E0766) will be denied as not reasonable and necessary.

A4555 ELECTRODE/TRANSDUCER FOR USE WITH ELECTRICAL STIMULATION DEVICE USED FOR CANCER TREATMENT, REPLACEMENT ONLY

E0766 ELECTRICAL STIMULATION DEVICE USED FOR CANCER TREATMENT, INCLUDES ALL ACCESSORIES, ANY TYPE

Policy article A52711 that supplements the LCD provides that "Tumor treatment field therapy devices are covered under the Durable Medical Equipment benefit (Social Security Act §1861(s)(6)). In order for a beneficiary's equipment to be eligible for reimbursement the reasonable and necessary (R&N) requirements set out in the related Local Coverage Determination must be met. In addition, there are specific statutory payment policy requirements, discussed below, that also must be met."

Further, the Policy Article States that "Code E0766 is in the frequent and substantial service payment category. Items included in this payment category are reimbursed a single monthly fee schedule amount for the device and all related supplies and accessories. Separate billing of supplies and/or accessories will be denied as unbundling."

Analysis

At issue in this case is whether reimbursement can be made for the TTFT therapy provided to the Beneficiary in four monthly applications from January 3, 2018 to April 3, 2018.

The Local Coverage Determination that addresses TTField therapy, L34823, specifically denies coverage. It states that tumor treatment field therapy (E0766) will be denied as not reasonable and

necessary. The LCD does not provide any circumstances under which TTField therapy would be covered.

The Beneficiary in this case has glioblastoma and was given a prescription by his treating physician to use TTField therapy following resection, radiation and chemotherapy. The Beneficiary, through his counsel, stated that he understands that there is an LCD that states that TTField therapy is not medically reasonable and necessary but notes that the last revision of the LCD L34832 was in 2013. The Beneficiary explained that the Optune therapy system that is at issue in this case was FDA approved for treatment of glioblastoma in 2015.

While we acknowledge that Medicare appropriately considered LCD L34832 in making the decision to deny the TTField therapy in this case based upon the unambiguous pronouncement that "tumor treatment field therapy (E0766) will be denied as not reasonable and necessary," we decline to follow that statement in the LCD. The Code of Federal Regulations identify the applicability of Local Coverage Determinations. It states that LCDs are required to be adhered to by Medicare contractors. (42 C.F.R. §405.1062). However, Administrative Law Judges and the Medicare Appeals Council are not bound by LCDs. If an ALJ declines to follow an LCD in a particular case, he or she may do so, but must explain why the policy was not followed. (*Id.*).

LCD L34832 does specifically state that TTField therapy will be denied as not reasonable and necessary. The tumor treatment field therapy that the Appellant is seeking is called "Optune." "Optune is a portable battery or power supply operated device which produces alternating electrical fields, called tumor treatment fields (TTFields) within the human body. The TTFields are applied to the patient's shaved head by means of electrically insulated surface transducer arrays, such that resistively coupled electric currents are not delivered to the patient. The TTFields disrupt the rapid cell division exhibited by cancer cells." https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034S013b.pdf. The peer-reviewed literature shows that tumor treating fields disrupt the cell division process in cancerous tumors which may lead to programmed cell death. Tumor treating fields have also shown statistically significant improvement in patient survival rates and outcomes in GBM brain tumors when compared with the traditional standard of care alone. While we acknowledge that the QIC appropriately considered LCD L34823 in making the decision to deny the Optune treatment in this case based upon the unambiguous pronouncement that the type of treatment is not reasonable and necessary, we feel we must decline to follow that statement in the LCD. No explanation was provided by the LCD for the failure to cover the TTField therapy. Certainly, the LCD is not required to include reasons for the denial of non-covered services. However, in giving an LCD its required deference when considering whether to abide by a pronouncement that is not binding on an ALJ, the reason for the non-coverage would be helpful to assess the applicability of the LCD. Here, we cannot determine the reasons for non-coverage but find that the rationales for finding coverage are extensive. In exercising our review authority, we hereby provide the bases for why we decline to follow the pronouncement in the LCD. (42 C.F.R. §405.1062(a)).

Without an explanation in the LCD as to why TTF therapy is considered as not medically reasonable and necessary, we are left to speculate. The TTFT was likely an emerging technology that had not been widely reviewed or tested for medical efficacy at the time the language was included in the LCD limiting its coverage. However, Optune was approved by the FDA for use in

the treatment of newly diagnosed glioblastoma on October 5, 2015¹. Moreover, at around the same time of the last LCD update, there were studies conducted and the results published passing on the efficacy of the use of TTField therapy, most notably the Optune (NovoTTF-100A therapy), for recurrent and new diagnoses of glioblastoma. *Stupp et al., NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomized phase III trial of a novel treatment modality*. Eur J Cancer. 2012 Sep; 48(14):2192-202. The results of further studies were presented in the Annual Meeting of the American Association for Cancer Research. *Stupp, Hegi, Idbaih, et al. Tumor treating fields added to standard chemotherapy in newly diagnosed glioblastoma (GBM): final results of a randomized, multicenter phase III trial*, Program and Abstracts of the 2017 Annual Meeting of the American Association for Cancer Research April 1-April 5, 2017 Washington, D.C. Abstract LBA AACR CT007. The results of these studies determined that Optune in combination with temozolomide was an effective treatment of this particular brain cancer, whether newly diagnosed or recurrent, that resulted in significant improvement in life expectancy of most patients.

We are also persuaded by the Beneficiary's medical provider. The Beneficiary's physician prescribed the treatment at issue in this case based upon the numerous studies and articles that described the medical effectiveness of Optune and based upon his own experience with the treatment.

On the basis of the foregoing, we decline to follow the LCD. The FDA approval of Optune, the overwhelming medical research evidence and the medical notes of the Beneficiary's physician discloses that Optune is effective in extending the lives of patients who have been newly diagnosed or have recurrent glioblastoma. We do not fault Medicare contractors for coming to a different conclusion. They adhered to the pronouncement in the LCD. However, if ever there was a reason for an ALJ to vary from the strict, unexplained pronouncement in an LCD, it is this case where the very life of the Beneficiary holds in the balance, with very few, if any, other medical options to treat him and prolong his life aside from the treatment provided by the Optune device.

Consequently, the undersigned finds that the Medicare requirements have been met. Accordingly, the ALJ finds that the TTFT treatment provided to the Beneficiary in this case are covered under Medicare Part B.

Conclusions of Law

Based on the foregoing, the undersigned concludes as a matter of law that the Optune Tumor Treatment Field Therapy services were shown to be medically reasonable and necessary and are covered under Medicare. The Beneficiary is entitled to reimbursement of the costs billed.

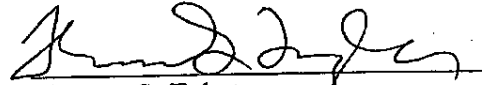
¹ https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034S013b.pdf

Order

The Medicare Contractor is **DIRECTED** to process the claim in accordance with this decision.

SO ORDERED.

Dated: 4/2/19


Thomas S. Tyler
U.S. Administrative Law Judge



Department of Health and Human Services
OFFICE OF MEDICARE HEARINGS AND APPEALS
Cleveland, Ohio

| | | |
|---------------|----------------|------------------------------------------------------------|
| Appeal of: | D. Christenson | OMHA Appeal No.: 1-8416270832 1-8416229632 |
| Beneficiary: | D. Christenson | Medicare Part B |
| Medicare No.: | *****3639A | Before: Richard J. Zettel U.S. Administrative Law Judge |

DECISION

After carefully considering the evidence and arguments presented in the record and at the hearing, a **FULLY FAVORABLE** decision is entered for the Appellant, D. Christenson.

Procedural History

The Appellant was treated with electronic stimulation cancer treatment, tumor treatment field therapy (CPT code E0766) (hereinafter referred to as "TTFT") on a monthly basis from May 3, 2018, through October 3, 2018 (Exhibit 2). *See*, Attachment A. The Provider of the TTFT was Novocure Inc. Claims for the TTFT were submitted to a Part B Durable Medical Equipment Medicare Administrative Contractor (DME MAC), which were denied initially and upon redetermination (Exhibit 1). On March 12, 2019, and March 19, 2019, a Qualified Independent Contractor (QIC), C2C Solutions, Inc., issued unfavorable reconsideration decisions (Exhibit 1, page 1). The QIC determined that LCD L34823 details that TTFT will be denied as not reasonable and necessary. The QIC held the Provider liable for the non-covered charges.

On March 29, 2019, the Appellant submitted timely requests for an Administrative Law Judge (ALJ) hearing to the Office of Medicare Hearings and Appeals (OMHA) (Exhibit 3, pages 5 and 1). On April 19, 2019, the Provider submitted a request for an ALJ hearing to the OMHA (Exhibit 3, pages 1 and 14). The amount in controversy meets the jurisdictional requirement for a hearing before OMHA in each appeal (Exhibit 1).

A telephonic hearing before the ALJ was held on May 15, 2019, in Cleveland, Ohio. Debra Parrish, Esq. appeared on behalf of the Appellant. Julie Miles, RN, Clinical Appeals Specialist,

1 of 9

OMHA-152

appeared on behalf of the Appellant and testified under oath. Exhibits 1-4 were admitted into the record in each appeal.

Issues

The ALJ is asked to decide whether the TTFT provided to the Appellant on multiple dates of service is reimbursable under Part B of Title XVIII of the Social Security Act, and if not, who is liable for the non-covered charges.

Findings of Fact

The attached Exhibit List is incorporated into this Decision by reference. The following facts are established by the preponderance of the evidence.

1. The Appellant was treated with electronic stimulation cancer treatment, tumor treatment field therapy (CPT code E0766) (hereinafter referred to as "TTFT") (also known as "Optune") on a monthly basis from May 3, 2018, through October 3, 2018 (Exhibit 2). *See*, Attachment A.
2. The Appellant was 63 years-old during the dates of service at issue (Exhibit 2, page 1).¹
3. On July 20, 2015, the Appellant underwent a right parietal occipital craniectomy (Exhibit 2, page 48). The biopsies of the right occipital brain tumor showed high grade glial tumor consistent
4. The record of the appeal includes office notes documenting the Appellant's treatment for glioblastoma multiforme, including surgery, radiation, and chemotherapy (Exhibit 2).
5. The Appellant received primary therapy with temozolomide and external beam radiation therapy (*Id.* and Exhibit 2, page 6). He had recurrence in the surgical bed roughly four months later and was treated with radiosurgery.
6. In 2016, the Appellant began using Optune therapy. *Id.* Since that time through September 19, 2018, the Appellant had been stable, if not improved in his imaging.
7. On September 18, 2018, an MRI of the brain revealed the following: stable postoperative findings of right craniotomy for right occipital tumor resection with unchanged appearance of the heterogeneously enhancing resection cavity; no evidence of tumor progression; flair hyperintense signal surround the resection cavity and extending throughout the right cerebral hemisphere; and unchanged mass effect with 4 mm midline shift to the left (Exhibit 2, page 8).
8. The plan was for the Appellant to continue on Optune therapy indefinitely (Exhibit 2, page 6).

¹ Exhibit numbers refer to OMHA Appeal No. 1-8416229632 unless otherwise specified.

9. Page two of three of the Optune Prescription Form was signed by the Appellant on September 22, 2016 (Exhibit 2, page 3).
10. Page one of five of the Optune Prescription Form was signed by the physician on November 29, 2017 (Exhibit 2, page 2). The prescription provides that the Beneficiary had a diagnosis of glioblastoma multiforme. The prescription provides that it was a renewal.
11. Page one of five of the Optune Prescription Form was signed by the physician on May 16, 2018 (Exhibit 2, page 1). The prescription provides that the Beneficiary had a diagnosis of recurrent GBM (glioblastoma multiforme).
12. Optune is FDA approved for recurrent and newly diagnosed glioblastoma multiforme brain tumors (Exhibit 4, page 7; Hearing testimony).
13. TTFT disrupts and corrupts the division of cancer cells and leads to the death of such cells. *Id.*
14. Peer-reviewed literature shows the improved clinical outcome of patients who receive TTFT for their glioblastoma (Exhibit 1 (both appeals); Hearing testimony).
15. TTFT for glioblastoma is included in the National Comprehensive Cancer Network (NCCN) guidelines (Exhibit 1, page 46). The NCCN guidelines for recurrent glioblastoma include "consider alternate electric field therapy for glioblastoma (Category 2B)."

Legal Framework

I. ALJ Review Authority

A. Jurisdiction

An individual who, or an organization that, is dissatisfied with the reconsideration of an initial determination is entitled to a hearing before the Secretary of the Department of Health and Human Services (HHS), provided there is a sufficient amount in controversy and a request for hearing is filed in a timely manner. Social Security Act (Act) § 1869(b)(1)(A).

In implementing this statutory directive, the Secretary has delegated the authority to administer the nationwide hearings and appeals system for the Medicare program to OMHA. The ALJs within OMHA issue the final decisions of the Secretary, except for decisions reviewed by the Medicare Appeals Council.

A hearing before an ALJ is only available if the remaining amount in controversy is \$160. 83 Fed. Reg. 47619 (Sept. 20, 2018) (setting the 2019 amount in controversy threshold amount at \$160). The request for hearing is timely if filed within sixty days after receipt of the QIC's reconsideration decision. *See*, 42 C.F.R. § 405.1002.

B. Scope of Review

"The issues before the ALJ include all the issues brought out in the initial determination, redetermination, or reconsideration that were not decided entirely in a party's favor. (For purposes of this provision, the term "party" does not include a representative of CMS or one of its contractors that may be participating in the hearing.) However, if evidence presented before the hearing causes the ALJ to question a favorable portion of the determination, he or she notifies the parties before the hearing and may consider it an issue at the hearing." See, 42 C.F.R. § 405.1032(a).

C. Standard of Review

Pursuant to § 557 of the Administrative Procedure Act ("APA"), an ALJ qualified and appointed pursuant to the APA acts as an independent finder of fact in conducting a hearing pursuant to § 1869 of the Act. The ALJ conducts a de novo review and issues a decision based on the hearing record. 42 C.F.R. § 405.1000(d).

II. Principles of Law

A. Social Security Act and Code of Federal Regulations

The Medicare program, Title XVIII of the Act, is administered through the Centers for Medicare and Medicaid Services, a component of the United States Department of Health and Human Services (HHS). Under the authority of Section 1842(a) (1) (A) of the Act, the Secretary of HHS is authorized to enter into contracts with private entities for the day-to-day operations of the program. For claims for durable medical equipment, prosthetics, orthotics, and supplies, DME MACs administer the processing of the claims.

Part B of Title XVIII of the Act, the Supplementary Medical Insurance program, provides coverage for a variety of medical services and supplies furnished by physicians, or by others in connection with physicians' services, for outpatient hospital services, and for a number of other specific health-related items and services. Individuals participate voluntarily in the Medicare Part B program and pay a monthly premium.

Section 1862(a)(1) of the Act excludes Medicare payment for services which "are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member".

Section 1834(a)(15)(C) of the Act provides that carriers shall, at the request of a supplier or beneficiary, determine in advance of delivery of an item whether payment for the item may not be made because the item is not covered if the item is a customized item, the patient to whom the item is to be furnished, or the supplier, requests that such advance determination be made, and the item is not an inexpensive item as specified by the Secretary.

Section 1832(a) of the Act states, in pertinent part: The benefits provided to an individual by the insurance program established by this part shall consist of

- (1) entitlement to have payment made to him or on his behalf (subject to the provisions of this part) for medical or other health services...

Section 1861(s) of the Act provides that the term "medical and other health services" includes durable medical equipment. 42 CFR § 414.202 defines durable medical equipment as equipment furnished by a supplier or a home health agency that-

- (1) can withstand repeated use;
- (2) is primarily and customarily used to serve a medical purpose;
- (3) generally is not useful to an individual in the absence of an illness or injury;
and
- (4) is appropriate for use in the home.

42 CFR § 410.38(a) provides in pertinent part as follows regarding the scope and conditions of durable medical equipment:

Medicare Part B pays for the rental or purchase of durable medical equipment, including iron lungs, oxygen tents, hospital beds, and wheelchairs, if the equipment is used in the patient's home or in an institution that is used as a home.

B. CMS Manual System and Local Policy

The manuals issued by the Centers for Medicare and Medicaid Services (CMS) administering the Medicare program also are considered. Although not binding on the ALJ, the respective manuals provide guidance in the administration of the Medicare program. In *Shalala v. Guernsey Memorial Hospital*, 514 U.S. 87, 102 (1995), the United States Supreme Court concluded that an agency manual section is a valid interpretive rule and that it is reasonable for the agency to follow it. CMS, *Medicare Benefit Policy Manual (MBPM) (Internet-Only Manual Publ'n 100-2)* ch. 15, § 110, provides general coverage guidelines for durable medical equipment.

CMS, *Medicare Program Integrity Manual (MPIM) (Internet-Only Manual Publ'n 100-8)* ch. 13, § 13.5.1 includes the follow guidance for contractors when drafting a proposed Local Coverage Determination (LCD):

In order to be covered under Medicare, a service shall be reasonable and necessary. When appropriate, contractors shall describe the circumstances under which the proposed LCD for the service is considered reasonable and necessary under 1862(a)(1)(A). Contractors shall consider a service to be reasonable and necessary if the contractor determines that the service is:

- Safe and effective;
- Not experimental or investigational (exception: routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary); and
- Appropriate, including the duration and frequency that is considered appropriate for the service, in terms of whether it is:
 - o Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;

- o Furnished in a setting appropriate to the patient's medical needs and condition;
- o Ordered and furnished by qualified personnel;
- o One that meets, but does not exceed, the patient's medical need; and
- o At least as beneficial as an existing and available medically appropriate alternative.

MPIM, supra ch. 13, § 13.7.1 continues as follows:

In order of preference, LCDs should be based on:

- Published authoritative evidence derived from definitive randomized clinical trials or other definitive studies, and
- General acceptance by the medical community (standard of practice), as supported by sound medical evidence based on:
 - o Scientific data or research studies published in peer-reviewed medical journals;
 - o Consensus of expert medical opinion (i.e., recognized authorities in the field); or
 - o Medical opinion derived from consultations with medical associations or other health care experts.

Acceptance by individual health care providers, or even a limited group of health care providers, normally does not indicate general acceptance by the medical community. Testimonials indicating such limited acceptance, and limited case studies distributed by sponsors with financial interest in the outcome, are not sufficient evidence of general acceptance by the medical community. The broad range of available evidence must be considered and its quality shall be evaluated before a conclusion is reached.

A Local Coverage Determination (LCD), as established by § 522 of the Benefits Improvement and Protection Act, is a decision by a fiscal intermediary or carrier whether to cover a particular service on an intermediary-wide or carrier-wide basis in accordance with § 1862(a)(1)(A) of the Act (i.e., a determination as to whether the service is reasonable and necessary). CGS Administrators and Noridian Healthcare Solutions, LLC issued Local Coverage Determination: Tumor Treatment Field Therapy (LCD L34823) (Jan. 2017), which provides in relevant part as follows: Tumor treatment field therapy (E0766) will be denied as not reasonable and necessary.

Analysis

The QIC determined that LCD L34823 details that TTFT will be denied as not reasonable and necessary. The QIC held the Provider liable for the non-covered charges. The Appellant argues that TTFT should be covered by Medicare. The ALJ disagrees with the findings of the QIC and determines that the TTFT provided to the Appellant is covered under Part B of Medicare.

Medicare is a defined benefit program, which means that it does not cover all available medical services and supplies. Medicare coverage is limited to those medical services and supplies identified by Congress, and by the Secretary of Health and Human Services and CMS in implementing Congressional directives. Medicare does not cover medical services that are not medically reasonable and necessary under § 1862(a)(1) of Act.

The QIC relied upon LCD L34823 to deny coverage for the TTFT for the Appellant. LCD L34823 provides that TTFT will be denied as not reasonable and necessary. Pursuant to 42 C.F.R. § 405.1062(a), an ALJ must give substantial deference to local coverage determinations. If an ALJ declines to follow a local coverage determination, the ALJ must explain the reason

why the policy was not followed in accordance with 42 C.F.R. § 405.1062(b). After careful consideration of the record and hearing testimony, the ALJ has decided to depart from LCD L34823 under the specific facts of this appeal.

First, the ALJ finds that LCD L34823 fails to identify any justification for the denial of all TTFT as not reasonable and necessary. Pursuant to *MPIM supra* ch. 13, §13.7.1, contractors shall consider a service to be reasonable and necessary if the contractor determines that the service is safe and effective. The record and hearing testimony support that TTFT is a safe and effective treatment of glioblastoma. Optune is FDA approved for recurrent and newly diagnosed glioblastoma multiforme brain tumors. TTFT disrupts and corrupts the division of cancer cells and leads to the death of such cells. Peer-reviewed literature shows the improved clinical outcome of patients who receive TTFT for their glioblastoma. TTFT for glioblastoma is included in the National Comprehensive Cancer Network guidelines. The NCCN guidelines for recurrent glioblastoma include "consider alternate electric field therapy for glioblastoma (Category 2B)." The Appellant pointed out that many payers are covering TTFT based on individual medical necessity review as well as published medical policy. *See*, Exhibits 1. Therefore, the ALJ will not afford substantial deference to LCD L34823 and concludes that TTFT is a safe and effective treatment of recurrent glioblastoma.

Second, the ALJ finds that the documentation and hearing testimony support that TTFT is medically reasonable and necessary to treat the Appellant. The Appellant was 63 years-old during the dates of service at issue. On July 20, 2015, the Appellant underwent a right parietal occipital craniectomy. The biopsies of the right occipital brain tumor showed high grade glial tumor consistent. The record of the appeal includes office notes documenting the Appellant's treatment for glioblastoma multiforme, including surgery, radiation, and chemotherapy. The Appellant received primary therapy with temozolomide and external beam radiation therapy. He had recurrence in the surgical bed roughly four months later and was treated with radiosurgery.

In 2016, the Appellant began using Optune therapy. Since that time through September 19, 2018, the Appellant had been stable, if not improved in his imaging. On September 18, 2018, an MRI of the brain revealed the following: stable postoperative findings of right craniotomy for right occipital tumor resection with unchanged appearance of the heterogeneously enhancing resection cavity; no evidence of tumor progression; flair hyperintense signal surround the resection cavity and extending throughout the right cerebral hemisphere; and unchanged mass effect with 4 mm midline shift to the left. The plan was for the Appellant to continue on Optune therapy indefinitely. Ms. Miles stated that the Appellant was diagnosed with brain cancer in July 2015 and was put on Optune. Ms. Miles said that the Appellant was still alive, which is phenomenal. Ms. Miles noted that the Appellant's compliance with therapy is excellent.

Based on the foregoing, the TTFT provided to the Appellant on the dates of service was medically reasonable and necessary. The TTFT provided to the Appellant from May 3, 2018, through October 3, 2018, is reimbursable under Part B of Medicare.

Conclusions of Law

The ALJ concludes that the TTFT provided to the Appellant on multiple dates of service was medically reasonable and necessary. Accordingly, the ALJ finds that the TTFT provided to the

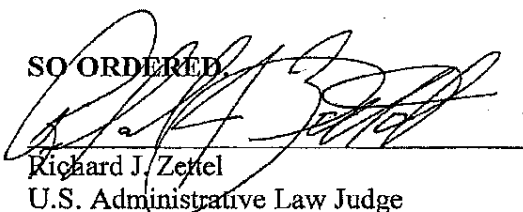
Appellant from May 3, 2018, through October 3, 2018, is reimbursable under Part B of Title XVIII of the Act. *See*, Attachment A.

Order

The Medicare Contractor is **DIRECTED** to process the claim in accordance with this decision.

Dated: June 6, 2019

SO ORDERED


Richard J. Zetzel
U.S. Administrative Law Judge

Enclosures:

Form OMHA-156, *List of Exhibits*

EXHIBIT 4



Department of Health and Human Services
Office of the Secretary

OFFICE OF MEDICARE HEARINGS AND APPEALS

Cleveland Field Office
200 Public Square, Suite 1300
Cleveland, OH 44114-2316
216-615-4000 (Main)
216-615-7546 (ALJ Watson Team)
216-615-6735 (Fax)
866-236-5089 (Toll Free)

July 1, 2019

D. CHRISTENSON
5754 CLEVEDON LN
OSHKOSH, WI 54904-9729

NOTICE OF HEARING

Appellant: **D. CHRISTENSON**
Beneficiary: **D. CHRISTENSON**
Medicare Number: *******3639A**
Date(s) of Service: **11/03/2018–11/03/2018**
OMHA Appeal Number: **1-8630709341**
Administrative Law Judge: **Scott Watson**

A hearing in the above appeal is scheduled for:

Hearing Date: **Wednesday August 28, 2019**
Hearing Time: **11:00 AM Eastern Time**

You are scheduled to appear by: ☒ Telephone
☐ Video-Teleconference (VTC)
☐ In-Person

Our office will call you on the hearing date at the time indicated above.

What do I do next?

You must respond to this notice within 5 calendar days of receipt. You are encouraged, but not required, to use the enclosed *Response to Notice of Hearing* (form OMHA-102) when responding. If you are a party to the appeal, your response must indicate whether you plan to attend the scheduled hearing, or whether you object to the proposed time and/or place of the hearing. If applicable, you must specify who else from your organization or entity plans to attend the hearing and in what capacity, and list any witnesses who will be providing testimony. If you are an employee of CMS or a CMS contractor and wish to attend the hearing as a participant, your response must indicate that you plan to attend the hearing and specify each individual who plans to attend.

What if I object to the type of hearing?

If you are a party to the appeal and you object to the type of hearing scheduled, please complete section 6 of the enclosed *Response to Notice of Hearing*, and indicate what type of hearing you would prefer (if you are also requesting to change the time of your scheduled hearing, see the section below titled "What if I can't attend my scheduled hearing?"). No explanation is required if you are an unrepresented beneficiary or enrollee requesting to appear by VTC. For all other requests for a VTC hearing, and any requests for an in-person hearing, you must explain why you object to the type of hearing scheduled. If the Administrative Law Judge changes the type of hearing, an amended notice of hearing will be sent to the parties and any potential participants who were sent a copy of this notice.

What if I can't attend my scheduled hearing?

If you are a party to the appeal and you cannot attend the hearing at the scheduled time and place, please call our office immediately at the direct dial phone number at the top of this notice. Please *also* complete section 4 of the enclosed *Response to Notice of Hearing* and explain why you are unable to attend the hearing at the scheduled time and place. If the Administrative Law Judge finds good cause to reschedule the hearing, an amended notice of hearing will be sent to the parties and any potential participants who were sent a copy of this notice.

What if I don't attend my scheduled hearing?

If you are the appellant and neither you nor your representative appears at the scheduled hearing, the Administrative Law Judge may dismiss your request for hearing unless good cause for the failure to appear is found. If you respond to this notice of hearing and fail to appear, you must contact the Administrative Law Judge within 10 calendar days after the hearing and provide a good cause reason for not appearing. If you do not respond to this notice of hearing and fail to appear, the Administrative Law Judge will send you a notice asking why you did not appear, and you will have 10 calendar days to respond. If you do not respond to the Administrative Law Judge's notice within 10 calendar days, or you do respond and the Administrative Law Judge determines you did not have good cause for failing to appear, your request for hearing will be dismissed. If the Administrative Law Judge determines that good cause exists, the hearing will be rescheduled and the time between the originally scheduled hearing date and new hearing date will not count toward the adjudication period.

What if I don't want a hearing?

If you are a party to the appeal, you have a right to appear at the hearing to present arguments in favor of your position, and offer testimony and evidence to the Administrative Law Judge. However, if you do not wish to present your case at a hearing, you may request a decision based on the written and other evidence in the record. To do so, please complete section 4 of the enclosed *Response to Notice of Hearing*. Please also complete and submit a *Waiver of Right to an Administrative Law Judge (ALJ) Hearing* (form OMHA-104). You can find a copy of this form online at www.hhs.gov/omha, or you may contact our office to receive a copy. Please note that your waiver does not affect the right of other parties to participate in the hearing and even if all parties waive the hearing, the Administrative Law Judge may still decide to conduct a hearing if it is necessary to decide the case. If a hearing is conducted and you do not attend, you may

still offer written evidence to the Administrative Law Judge. Please see below for additional information regarding the submission of evidence.

What if I no longer wish to pursue this appeal?

If you decide that you no longer wish to pursue this appeal, you may withdraw your request for hearing in writing. You may do this by letter or by completing and submitting a *Withdrawal of Request for an Administrative Law Judge Hearing* (form OMHA-119). You can find a copy of this form online at www.hhs.gov/omha, or you may contact our office to receive a copy. If you submit a written request for withdrawal and no other party has filed a valid request for hearing, your appeal will be dismissed. Your request to withdraw will not be honored if a decision, dismissal or remand has already been issued.

What issues will be addressed at the hearing?

The issues before the Administrative Law Judge include all of the issues brought out in the initial determination, coverage determination, or organization determination; redetermination; or reconsideration that were not decided entirely in a party's favor, for the claims or other appealed matters specified in the request for hearing.

What if I object to the issues listed above?

If you are a party and you object to the issues, you must notify the Administrative Law Judge in writing at the earliest possible opportunity before the time set for the hearing and explain your objections. You can either do this in section 6 of the enclosed *Response to Notice of Hearing* or at a later time, but no later than 5 calendar days before the date of your scheduled hearing. You must send a copy of your objections to all the parties who were sent a copy of this notice and to CMS or any CMS contractor that has elected to be a party to the hearing. The Administrative Law Judge will make a decision on your objections either in writing, at a prehearing conference, or at the hearing.

Can I have a representative?

Yes. You have the right to have a representative attend the hearing on your behalf or attend the hearing with you. You can be represented by an attorney or other person. If you have a representative and have not completed and submitted an *Appointment of Representative* (form CMS-1696), which can be found online at www.hhs.gov/omha, or other written statement authorizing your representative to act on your behalf, please call our office as soon as possible.

Can I request a copy of the case file?

Yes. If you would like a copy of all or part of your file before the date of the hearing, please contact our office for further instructions.

Can I submit additional evidence?

If you want to submit additional written or other evidence, please complete and submit a *Filing of New Evidence* (form OMHA-115). You can find a copy of this form online at www.hhs.gov/omha, or you may contact our office to receive a copy. Unless you are an

unrepresented beneficiary or enrollee, you must submit all evidence by the date (if any) you have specified in your request for hearing, or within 10 calendar days of receiving this notice. If evidence is submitted more than 10 calendar days after receiving this notice, any applicable adjudication period will be extended by the number of calendar days in the period between 10 calendar days after receipt of this notice and the day the evidence is received. Please note that although the 10-day submission time frame does not apply to unrepresented beneficiaries and enrollees, they may wish to submit any additional evidence as soon as possible to allow the Administrative Law Judge more time to consider the evidence before the hearing.

If you are a provider or supplier, or a beneficiary represented by a provider or supplier, and you are appealing a reconsideration issued by a Medicare Part A or Part B Qualified Independent Contractor (QIC), you must also submit a statement explaining why the evidence was not submitted prior to the issuance of the QIC's reconsideration. The Administrative Law Judge will determine whether you have good cause for submitting the evidence for the first time at the OMHA level of appeal.

Will any experts participate or testify at the hearing?

No experts are scheduled to testify at your hearing.

What happens at the hearing?

- The Administrative Law Judge will open the hearing and ask the parties, participants and any representatives to identify themselves and any witnesses they may be calling;
- The Administrative Law Judge will ask you and any other witnesses to take an oath or to affirm that the testimony is true;
- You will have the opportunity to present facts and arguments;
- If you are a party, you or your representative may present witnesses and may cross-examine the witnesses of the other parties;
- The Administrative Law Judge may question you and any other witnesses about the facts and issues;
- The Administrative Law Judge may allow you to submit additional written statements and affidavits about the matter in lieu of testimony or argument at the hearing. You must submit the additional statements and affidavits within the time frame designated by the Administrative Law Judge and provide a copy of them to the other parties to your hearing, if any, at the same time you submit them to the Administrative Law Judge;
- The Administrative Law Judge will review the issue(s) and entire record of your claim, independent of any determinations previously made on your claim; and
- The Administrative Law Judge will make an audio recording of the hearing.

How will I know the result of my case?

After the hearing, the Administrative Law Judge will issue a written decision, which will be mailed to all parties to the appeal, the relevant QIC or Independent Review Entity, and the Part D plan sponsor if you are appealing a Part D coverage determination. The decision will include findings of fact, conclusions of law, and the reasons for the decision. The Administrative Law Judge will base the decision on the evidence of record, including the testimony at the hearing.

Whom do I contact with other questions about my hearing?

If you have any questions about your hearing, please call or write our office. A direct-dial telephone number and mailing address are at the top of this notice. Please provide the Administrative Law Judge name and OMHA appeal number if you write to the office, or have the information available if you call.

cc:

DEBRA M PARRISH
788 WASHINGTON RD
PITTSBURGH, PA 15228

C2C Innovative Solutions, Inc.
DME QIC Appeals-ALJ
P.O. Box 44006
Jacksonville, FL 32231-4006

NOVOCURE INC.
195 Commerce Way
Portsmouth, NH 03801

Enclosures:

OMHA-102, Response to Notice of Hearing



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Office of Medicare Hearings and Appeals

RESPONSE TO NOTICE OF HEARING

Instructions: Complete sections 2 through 8 below, as applicable, and return this form to the assigned Administrative Law Judge (ALJ) **within 5 days of receiving the notice of hearing**. For expedited Part D hearings, contact the ALJ at the telephone number provided at the top of the notice of hearing or complete and return this form to the ALJ **within 2 days of receiving the notice of hearing**. The return mailing address and fax number are at the top of the notice of hearing. You do not need to include the notice of hearing with your response.

Please note that only a party to the hearing may call witnesses; object to the time, place, or type of hearing; object to the statement of issues to be decided at the hearing; or object to the assigned ALJ (sections 4 through 6 below). Non-party participants are not permitted to call witnesses and may not file objections.

Section 1: Hearing information. [TO BE COMPLETED BY THE OFFICE OF MEDICARE HEARINGS AND APPEALS]

| | | | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|--------------------------------------------------------|----------------|
| OMHA Appeal Number 1-8630709341 | | Appellant D. CHRISTENSON | |
| Type of Hearing <input checked="" type="checkbox"/> Telephone <input type="checkbox"/> Video-Teleconference (VTC) <input type="checkbox"/> In-Person | | Assigned ALJ Scott Watson | |
| Hearing Day of Week Wednesday | Hearing Date 08/28/2019 | Hearing Time 11:00 AM Eastern Time | |
| Telephone Hearing Call-in Number (if applicable) | | Passcode or Collaboration Code (for telephone hearing) | |
| VTC or In-Person Hearing Address (if applicable) | | City | State ZIP Code |

Section 2: What is the responding party's or participant's information? (Representative information in next section)

| | | | |
|------------------------------------|--------------------------------------|------------------|----------|
| Name (First, Middle initial, Last) | Firm or Organization (if applicable) | Telephone Number | |
| Mailing Address | City | State | ZIP Code |

If the respondent is an entity or organization, please list all individuals who plan to attend the hearing and the capacity in which they are attending:

Section 3: What is the representative's information? (Skip if you do not have a representative)

| | | | |
|-----------------|--------------------------------------|------------------|----------|
| Name | Firm or Organization (if applicable) | Telephone Number | |
| Mailing Address | City | State | ZIP Code |

Section 4: Will you be present at the time and place shown above? (Check one)

- ☐ I will be present at the time and place shown on the notice of hearing. If an emergency arises after I submit this response and I cannot be present, I will notify the ALJ at the telephone number shown at the top of the notice of hearing as soon as possible.
- ☐ I cannot be present at the time and place shown on the notice of hearing and would like to request that my hearing be rescheduled. I understand that the ALJ has the discretion to change the time and place of the hearing as long as my explanation for my request to reschedule meets the good cause standard for changing the time and place of the hearing. (For example, good cause may be found due to an inability to attend the hearing because of a serious physical or mental condition, incapacitating injury, or death in the family or if severe weather conditions make it impossible to travel to the hearing. See 42 C.F.R. sections 405.1020(f) and (g), and 42 C.F.R. sections 423.2020(f) and (g) for additional circumstances that may establish good cause.) I understand that if I am the appellant and the hearing is postponed at my request, the time between the originally scheduled hearing date and the new hearing date is not counted toward any applicable adjudication period.

I would like to reschedule my hearing for the following date and time, and I have good cause to reschedule my hearing because:

☐ I want to waive my right to appear at the ALJ hearing. (Please complete form OMHA-104 and attach it to this response.)

Section 5: Do you intend to call any witnesses to provide testimony at the hearing?

- ☐ No.
- ☐ Yes, I intend to call the following witnesses (attach a continuation sheet if necessary):

Section 6: Do you object to any of the following conditions? (Check all that apply)

- ☐ **I object to the type of hearing scheduled.** If you are an unrepresented beneficiary or enrollee, and a telephone hearing is scheduled, you have the right to request that a VTC hearing be held instead if VTC technology is available. For all other parties, if a telephone hearing is scheduled, the ALJ may find good cause for an appearance by VTC if he or she determines that VTC is necessary to examine the facts or issues involved in the appeal.

If a telephone or VTC hearing is scheduled and the party, including an unrepresented beneficiary or enrollee, requests that an in-person hearing be held instead, the ALJ, with the agreement of the Chief ALJ or designee, may find good cause for an in-person hearing if VTC or telephone technology is not available, or if special or extraordinary circumstances exist.

I object to the type of hearing scheduled and request a (check one) ☐ VTC or ☐ in-person hearing because:

Note: No explanation is required if you are an unrepresented beneficiary or enrollee requesting a VTC hearing.

- ☐ **I object to the issues described in the notice of hearing.** I understand that I must send a copy of my objection to the issues to all the other parties who were sent a copy of the notice of hearing, and to CMS or a CMS contractor that elected to be a party to the hearing (if you do not have these addresses, please contact the ALJ's adjudication team at the telephone number shown at the top of the notice of hearing). I understand that the ALJ will make a decision on my objection either in writing, at a prehearing conference, or at the hearing.

I object to the issues described in the notice of hearing because:

- ☐ **I object to the ALJ assigned to my appeal.** I understand that an ALJ cannot adjudicate an appeal if he or she is prejudiced or partial with respect to any party or has an interest in the matter pending for decision, and that I may object to the ALJ assigned to my appeal for these reasons. I understand that the ALJ will consider my objection and decide whether to proceed with the appeal or withdraw. I understand that if I object to the ALJ assigned to my appeal, and the ALJ subsequently withdraws from the appeal, another ALJ will be assigned, and any applicable adjudication time frame will be extended by 14 calendar days.

I object to the assigned ALJ because:

Section 7: If you are the appellant, do you want to waive or extend the time frame to decide your appeal? (If yes, check one)

- ☐ **I want to waive the time frame for the ALJ to decide my appeal.** I understand that by waiving this time frame, the ALJ does not have to decide my appeal within any applicable adjudication period that would otherwise apply.
- ☐ **I want to extend the time frame for the ALJ to decide my appeal.** I want the time frame to be extended _____ calendar days beyond any applicable adjudication period.

Section 8: Sign and date this form.

Party, Participant or Representative Signature

Date

Privacy Act Statement

The legal authority for the collection of information on this form is authorized by the Social Security Act (section 1155 of Title XI and sections 1852(g)(5), 1860D-4(h)(1), 1869(b)(1), and 1876 of Title XVIII). The information provided will be used to further document your appeal. Submission of the information requested on this form is voluntary, but failure to provide all or any part of the requested information may affect the determination of your appeal. Information you furnish on this form may be disclosed by the Office of Medicare Hearings and Appeals to another person or governmental agency only with respect to the Medicare Program and to comply with Federal laws requiring the disclosure of information or the exchange of information between the Department of Health and Human Services and other agencies.

If you need large print or assistance, please call 1-855-556-8475



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Office of Medicare Hearings and Appeals

RESPONSE TO NOTICE OF HEARING

Instructions: Complete sections 2 through 8 below, as applicable, and return this form to the assigned Administrative Law Judge (ALJ) within 5 days of receiving the notice of hearing. For expedited Part D hearings, contact the ALJ at the telephone number provided at the top of the notice of hearing or complete and return this form to the ALJ within 2 days of receiving the notice of hearing. The return mailing address and fax number are at the top of the notice of hearing. You do not need to include the notice of hearing with your response.

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Section 1: Hearing information. [TO BE COMPLETED BY THE OFFICE OF MEDICARE HEARINGS AND APPEALS]

| | | | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|--------------------------------------------------------|----------------|
| OMHA Appeal Number 1-8630709341 | Appellant D. CHRISTENSON | | |
| Type of Hearing <input checked="" type="checkbox"/> Telephone <input type="checkbox"/> Video-Teleconference (VTC) <input type="checkbox"/> In-Person | | Assigned ALJ Scott Watson | |
| Hearing Day of Week Wednesday | Hearing Date 08/28/2019 | Hearing Time 11:00 AM Eastern Time | |
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| VTC or In-Person Hearing Address (if applicable) | | City | State ZIP Code |

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| | | | |
|------------------------------------|--------------------------------------|------------------|----------|
| Name (First, Middle initial, Last) | Firm or Organization (if applicable) | Telephone Number | |
| Mailing Address | City | State | ZIP Code |

If the respondent is an entity or organization, please list all individuals who plan to attend the hearing and the capacity in which they are attending:

Section 3: What is the representative's information? (Skip if you do not have a representative)

| | | | |
|-----------------------------------------------|--------------------------------------------------------------------|-----------------------------------------|--------------------------|
| Name Debra M. Parrish | Firm or Organization (if applicable) Parrish Law Offices | Telephone Number 412-561-6250 | |
| Mailing Address 788 Washington Road | City Pittsburgh | State PA | ZIP Code 15228 |

Section 4: Will you be present at the time and place shown above? (Check one)

- ☒ I will be present at the time and place shown on the notice of hearing. If an emergency arises after I submit this response and I cannot be present, I will notify the ALJ at the telephone number shown at the top of the notice of hearing as soon as possible.
- ☐ I cannot be present at the time and place shown on the notice of hearing and would like to request that my hearing be rescheduled. I understand that the ALJ has the discretion to change the time and place of the hearing as long as my explanation for my request to reschedule meets the good cause standard for changing the time and place of the hearing. (For example, good cause may be found due to an inability to attend the hearing because of a serious physical or mental condition, incapacitating injury, or death in the family or if severe weather conditions make it impossible to travel to the hearing. See 42 C.F.R. sections 405.1020(f) and (g), and 42 C.F.R. sections 423.2020(f) and (g) for additional circumstances that may establish good cause.) I understand that if I am the appellant and the hearing is postponed at my request, the time between the originally scheduled hearing date and the new hearing date is not counted toward any applicable adjudication period.

I would like to reschedule my hearing for the following date and time, and I have good cause to reschedule my hearing because:

☐ I want to waive my right to appear at the ALJ hearing. (Please complete form OMHA-104 and attach it to this response.)

Section 5: Do you intend to call any witnesses to provide testimony at the hearing?

- ☐ No.
- ☒ Yes, I intend to call the following witnesses (attach a continuation sheet if necessary):
 Tim Parks, RN, Clinical Appeals Specialist 603-570-9398

Section 6: Do you object to any of the following conditions? (Check all that apply)

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- ☐ I object to the ALJ assigned to my appeal. I understand that an ALJ cannot adjudicate an appeal if he or she is prejudiced or partial with respect to any party or has an interest in the matter pending for decision, and that I may object to the ALJ assigned to my appeal for these reasons. I understand that the ALJ will consider my objection and decide whether to proceed with the appeal or withdraw. I understand that if I object to the ALJ assigned to my appeal, and the ALJ subsequently withdraws from the appeal, another ALJ will be assigned, and any applicable adjudication time frame will be extended by 14 calendar days.

I object to the assigned ALJ because:

Section 7: If you are the appellant, do you want to waive or extend the time frame to decide your appeal? (If yes, check one)

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- ☐ I want to extend the time frame for the ALJ to decide my appeal. I want the time frame to be extended _____ calendar days beyond any applicable adjudication period.

Section 8: Sign and date this form.

Party, Participant or Representative Signature

Date

7/5/2019

Privacy Act Statement

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If you need large print or assistance, please call 1-855-556-8475

DEBRA M. PARRISH, P.C.
788 WASHINGTON ROAD
PITTSBURGH, PA 15228
PHONE: (412) 561-6250
FAX: (412) 561-6253

FAX TRANSMITTAL

TO: Judge Watson

FAX NO.: 216-615-6735

FROM: Debra M. Parrish

DATE: July 5, 2019

TOTAL NUMBER OF PAGES INCLUDING COVER LETTER: 3

Please contact Tanya Terza at (412) 561-6250 if there is a problem with transmission.

RE: Response to Notice of Hearing
Beneficiary: D. Christenson
Appellant: D. Christenson
ALJ Appeal No. 1-8630709341
Our Reference: 19-296

ALJ Watson Team:

Please find attached the Response to Notice of Hearing for the above-captioned case. If you have any questions, please do not hesitate to contact us at (412) 561-6250.

Kind regards,
Debra M. Parrish
Bridget Noonan
Phone: (412) 561-6250
Fax: (412) 561-6253

This facsimile transmission contains PRIVILEGED AND CONFIDENTIAL INFORMATION intended only for the use of the Addressee(s) named above. If you are not the intended recipient of this facsimile, or the employee or agent responsible for delivering it to the intended recipient, you are hereby notified that any dissemination or copying of this facsimile is strictly prohibited. If you have received this facsimile in error, please immediately notify us by telephone and return the original facsimile to us at the address above via the U.S. Postal Service. Thank you.

EXHIBIT 3

JUN 17 2019 SW

OPERATIONS WFO

PARRISH LAW OFFICES

788 WASHINGTON ROAD
PITTSBURGH, PENNSYLVANIA 15228-2021
www.dparrishlaw.com

June 14, 2019

412.561.6250
FAX 412.561.6253
E-mail: info@dparrishlaw.com

VIA PRIORITY MAIL

DHHS – OMHA

Centralized Docketing

Attn: Beneficiary Mail Stop

200 Public Square, Suite 1260

Cleveland, OH 44114-2316

BENEFICIARY APPEAL**RE: Request for ALJ Hearing****Beneficiary: David Christenson****5754 Clevedon Lane****Oshkosh, WI 54904****Dates of Service: 11/3/2018; 12/3/2018; 1/3/2019****HICN: 7QR9QM0QP33****Medicare Appeal No: 1-8486340738****Date of QIC Decision: June 7, 2019****Device: Tumor Treatment Field Therapy (E0766)****Supplier: Novocure, Inc.****Our Ref: 19-296**

Dear Claims Coordinator:

As an authorized representative of the above-captioned Medicare beneficiary, David Christenson, I hereby appeal to an Administrative Law Judge the above-captioned decision rendered by the Qualified Independent Contractor ("QIC") C2C Innovative Solutions, Inc. for the claims submitted for tumor treatment field therapy ("TTFT") for a glioblastoma. The QIC rendered a nonsensical denial stating, "the medical documentation of the efficacy of this device is not within the usual scope and breath (sic) of current medical literature with peer acknowledgement and review." The QIC also asserts that although the DMACs acknowledged a valid reconsideration request was filed, LCD L34823 remains applicable until the DMACs retire it or issue a new LCD.

Mr. Christenson is a Medicare beneficiary who has been married for 41 years. He has two children and two grandchildren was diagnosed with a glioblastoma in 2016. He had surgery and was treated with radiation and chemotherapy. His clinician also prescribed TTFT and began using it in October 2016. During the clinical trial for newly diagnosed glioblastomas and a first recurrent, such as that of Mr. Christenson, the TTFT results were so compelling that at the interim analysis, the Data Safety Monitoring Board recommended that those not receiving TTFT be able to cross over to receive the treatment. The FDA agreed.

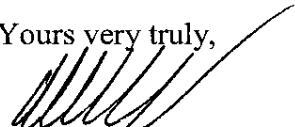
The published, peer-reviewed literature shows the improved clinical survival and the progression-free survival of patients who receive TTFT for their glioblastoma. TTFT for glioblastoma is included in the National Comprehensive Cancer Network ("NCCN") guidelines and is considered the standard of care for newly diagnosed glioblastoma. Hundreds of treating physicians, in all 50 states, have prescribed TTFT. TTFT is covered by all the large national payers: Medicare has paid for numerous claims for medically indistinguishable beneficiaries.

The QIC's determination does not make sense. The seminal articles showing the effectiveness of the treatment/device were published in JAMA, one of the most prestigious journals in the country based on "impact factor." JAMA is a peer-reviewed publication, thus the assertion that the documentation lacks review is belied by the evidence. Multiple peer-reviewed articles show the effectiveness of the device, to the QIC's comment regarding scope and breadth. The inclusion of TTFT in the NCCN guidelines is "peer acknowledgment and review."

Contrary to the QIC's assertion, on May 9, 2019, the DMACs have issued a draft LCD that extends TTFT coverage to GBM. Further, on May 28, 2019 the Civil Remedies Division ruled that the LCD record did not support the validity of the LCD under the reasonableness standard. TTFT meets Medicare coverage criteria and the QIC's decision fails to acknowledge the evidence showing the LCD is invalid.

Finally, Medicare coverage for Mr. Christenson has already been decided. Mr. Christenson received a favorable ALJ ruling on the prior dates of service.

Yours very truly,



Debra Parrish on behalf of
Mr. David Christenson

Enclosures:

Attachment A: Appointment of Representative Form
Attachment B: Certificate of Service

cc: Mr. David Christenson
Novocure, Inc., c/o Justin Kelly

APPOINTMENT OF REPRESENTATIVE

| | |
|-------------------------------------|-----------------------------------------------------------------|
| NAME OF PARTY: David Christenson | MEDICARE OR NATIONAL PROVIDER IDENTIFIER NUMBER: 7QR9QM0QP33 |
|-------------------------------------|-----------------------------------------------------------------|

SECTION I: APPOINTMENT OF REPRESENTATIVE

To be completed by the party seeking representation (i.e., the Medicare beneficiary, the provider or the supplier):

I appoint this individual: Debra M. Parrish to act as my representative in connection with my claim or asserted right under Title XVIII of the Social Security Act (the "Act") and related provisions of Title XI of the Act. I authorize this individual to make any request; to present or to elicit evidence; to obtain appeals information; and to receive any notice in connection with my appeal, wholly in my stead. I understand that personal medical information related to my appeal may be disclosed to the representative indicated below.

| | | |
|------------------------------------------------------------------------|--------------|--------------------------------------------------|
| SIGNATURE OF PARTY SEEKING REPRESENTATION: <i>David Christenson</i> | | DATE: 1/26/2019 |
| STREET ADDRESS: 5754 Clevedon Lane | | PHONE NUMBER (with Area Code): (920) 203-5636 |
| CITY: Oshkosh | STATE: WI | ZIP: 54904 |

SECTION II: ACCEPTANCE OF APPOINTMENT

To be completed by the representative:

I, Debra M. Parrish, hereby accept the above appointment. I certify that I have not been disqualified, suspended, or prohibited from practice before the Department of Health and Human Services; that I am not, as a current or former employee of the United States, disqualified from acting as the party's representative; and that I recognize that any fee may be subject to review and approval by the Secretary.

I am a / an ATTORNEY (Debra M. Parrish)

(PROFESSIONAL STATUS OR RELATIONSHIP TO THE PARTY, E.G. ATTORNEY, RELATIVE, ETC.)

| | | |
|----------------------------------------------------|--------------|--------------------------------------------------|
| SIGNATURE OF REPRESENTATIVE: <i>[Signature]</i> | | DATE: 2-5-19 |
| STREET ADDRESS: 788 Washington Road | | PHONE NUMBER (with Area Code): (412) 561-6250 |
| CITY: Pittsburgh | STATE: PA | ZIP: 15228 |

SECTION III: WAIVER OF FEE FOR REPRESENTATION

Instructions: This section must be completed if the representative is required to, or chooses to waive their fee for representation. (Note that providers or suppliers that are representing a beneficiary and furnished the items or services may not charge a fee for representation and must complete this section.)

I waive my right to charge and collect a fee for representing _____ before the Secretary of the Department of Health and Human Services.

| | |
|-----------|------|
| SIGNATURE | DATE |
|-----------|------|

SECTION IV: WAIVER OF PAYMENT FOR ITEMS OR SERVICES AT ISSUE

Instructions: Providers or suppliers serving as a representative for a beneficiary to whom they provided items or services must complete this section if the appeal involves a question of liability under section 1879(a)(2) of the Act. (Section 1879(a)(2) generally addresses whether a provider/supplier or beneficiary did not know, or could not reasonably be expected to know, that the items or services at issue would not be covered by Medicare.)

I waive my right to collect payment from the beneficiary for the items or services at issue in this appeal if a determination of liability under §1879(a)(2) of the Act is at issue.

| | |
|-----------|------|
| SIGNATURE | DATE |
|-----------|------|

CERTIFICATE OF SERVICE

I hereby certify that I sent a copy of the request for hearing and all attachments submitted on behalf of Mr. David Christenson to the following parties via the following methods on June 14, 2019

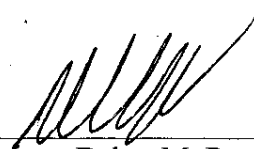
USPS First Class Mail:

Mr. David Christenson
5754 Clevdon Lane
Oshkosh, WE 54904

Electronic Mail [via secure server]:

Novocure, Inc.
c/o Justin Kelly
JKelly@novocure.com
195 Commerce Way
Portsmouth, NH 03801

June 14, 2019



Debra M. Parrish
Parrish Law Offices

**THERE ARE THREE
SEPARATE
BENEFICIARY
REQUESTS
FOR HEARING IN
THIS ENVELOPE**

JUN 17 2019 SW

OPERATIONS DIV

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| Electronic Rate Approved #038555749 | | | |



USPS.COM/PICKUP

EP14F Oct 2018
OD: 12 1/2 x 9 1/2



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UNITEL POSTAL

UNIT MAIL

Delivery specified*
PACKING™ included to n
destinations.
International insurance.
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label may be required
only



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Office of Medicare Hearings and Appeals

INTEROFFICE TRANSMITTAL

Instructions: This form is used to document the interoffice transmittal of records in an appeal pending at the Office of Medicare Hearings and Appeals (OMHA). Attach this form to any materials sent between OMHA offices because they were submitted to an incorrect office. The receiving office must date stamp the enclosed materials upon receipt and associate them with the administrative record for the appeal. This form must be retained with the enclosed materials in the administrative record.

Section 1: What is the appeal information?

| | |
|------------------------------------|----------------------------------------------------------|
| OMHA Appeal Number 1-8630709341 | Reconsideration Appeal Number (if no OMHA appeal number) |
| Appellant Novocure, Inc. | OMHA Adjudicator (if assigned) Judge Watson |

Section 2: What is the OMHA sender's information?

| | |
|------------------------------------|-------------------------|
| Sending OMHA Office Central Ops | Date of Initial Receipt |
|------------------------------------|-------------------------|

Section 3: What is the OMHA recipient's information?

| | |
|------------------------------------|---------------------------|
| Receiving OMHA Office Cleveland | Attention (if applicable) |
|------------------------------------|---------------------------|

Section 4: Provide a brief description of the enclosed materials below.

Supplemental documentation.

RECEIVED
JUL 08 2019
BY: _____

REQUEST FOR MEDICARE HEARING BY AN ADMINISTRATIVE LAW JUDGE

☐ Part A
☒ Part B

Effective July 1, 2005. For use by party to a reconsideration determination issued by a Qualified Independent Contractor (QIC)
(Amount in controversy must be \$100 or more.)

Send copies of this completed form to:

Original — Office of Medicare Hearings and Appeals Field Office specified in the QIC Reconsideration Notice

Copy — Appellant **Copy** — All other parties

Failure to send a copy of this completed request to the other parties to the appeal will delay the start date of your appeal.

Did you send all required copies? ☒ Yes ☐ No

OMHA CENTRAL

JUL 01 2019 TD

OPERATION DIV.

Appellant (The party appealing the reconsideration determination)

NOVOCURE, INC

Beneficiary (Leave blank if same as the appellant.)

David Christenson

Provider or Supplier (Leave blank if same as the appellant.)

Novocure Inc.

Address

5754 Clevedon Lane

Address

195 Commerce Way

City

Oshkosh

State

WI

Zip Code

54904

City

Portsmouth

State

NH

Zip Code

03801

Area Code/Telephone Number

(920) 203-5636

E-mail Address

Area Code/Telephone Number

603-617-4756

E-mail Address

dmccoy@novocure.com

Insurance (Medicare) Claim Number

1483639A

Document control number assigned by the QIC

1-8486340738

QIC that made the reconsideration determination

C2C Solutions

Dates of Service

From 11/03/2018 01/03/2019

I DISAGREE WITH THE DETERMINATION MADE ON MY APPEAL BECAUSE:

Novocure is an accredited CMS DMEPOS supplier by the Accreditation Commission for Healthcare and is a CMS supplier for

Durable Medical equipment. In addition, attached is a letter of medical necessity, FDA approval, NCCN and Clinical.

You have a right to be represented at the hearing. If you are not represented but would like to be, your Office of Medicare Hearings and Appeals Field Office will give you a list of legal referral and service organizations. (If you are represented and have not already done so, complete form CMS-1696.)

Check ☒ I **wish** to have a hearing.
Only One ☐ I **do not wish** to have a hearing and I request that a
Statement: decision be made on the basis of the evidence in my case. (Complete form HHS-723, "Waiver of Right to an ALJ Hearing.")

Check ☐ I **have** additional evidence to submit.
Only One ☒ I **have no** additional evidence to submit.
Statement:

If you have additional evidence to submit, please attach the evidence or attach a statement explaining what you intend to submit and when you intend to submit it. If you are a provider, supplier, or beneficiary represented by a provider or supplier, the evidence must be accompanied by a good cause statement explaining why the evidence is being submitted for the first time at the ALJ level.

The appellant should complete No. 1 and the representative, if any, should complete No. 2. If a representative is not present to sign, print his or her name in No. 2. Where applicable, check to indicate if appellant will accompany the representative at the hearing. ☐ Yes ☒ No

1. (Appellant's Signature)

Date: 06/21/2019

2. (Representative's Signature/Name)

Date

Address

195 Commerce Way

Address

☐ Attorney

☒ Non-Attorney

City

Portsmouth

State

NH

Zip Code

03801

City

State

Zip Code

Area Code/Telephone Number

603-617-4756

E-mail Address

dmccoy@novocure.com

Area Code/Telephone Number

E-mail Address

Answer the following questions that apply:

- A) Does request involve multiple claims? (If yes, a list of all the claims must be attached.)
B) Does request involve multiple beneficiaries? (If yes, a list of beneficiaries, their HICNs and the dates of service.)
C) Did the beneficiary assign his or her appeal rights to you as the provider/supplier?
(If yes, you must complete and attach form CMS-20031. Failure to do so will prevent approval of the assignment.)

☒ Yes ☐ No
☐ Yes ☒ No
☐ Yes ☒ No

Must be completed by the provider/supplier if representing the beneficiary:

I waive my rights to charge and collect a fee for representing David Christenson before the Office of Medicare Hearings and Appeals. (Beneficiary name)

Signature of provider/supplier representing beneficiary

Date: 06/21/2019

Must be completed by the provider/supplier if representing the beneficiary, they furnished the item(s) or services(s) at issue, and the appeal involves a question of liability under section 1879(a)(2) of the Social Security Act:

I waive my right to collect payment from the beneficiary for the furnished items or services at issue involving 1879(a)(2) of the Social Security Act.

Signature of provider/supplier representing beneficiary

Date: 06/21/2019

TO BE COMPLETED BY THE OFFICE OF MEDICARE HEARINGS AND APPEALS

Is this request filed timely? ☐ Yes ☐ No

If no, attach appellant's explanation for delay. If there is no explanation, send a Notice of Late Filing of Request for ALJ Hearing to the appellant and representative, if applicable, to request such an explanation.

| | | |
|---------------------|--------------|-------------|
| Request received on | Field Office | Employee |
| Assigned on | Assigned by | Assigned to |

Special response case? ☐ Yes ☐ No

If yes, explain why and state the targeted adjudication deadline.

Interpreter/translator needed (including sign language) ☐ Yes ☐ No

If yes, type needed:

If appellant not represented, has a list of legal referral and service organizations been provided. ☐ Yes ☐ No

PRIVACY ACT STATEMENT

The legal authority for the collection of information on this form is authorized by the Social Security Act (section 1155 of Title XI and sections 1852(g)(5), 1860D-4(h)(1), 1869(b)(1), and 1876 of Title XVIII). The information provided will be used to further document your appeal. Submission of the information requested on this form is voluntary, but failure to provide all or any part of the requested information may affect the determination of your appeal. Information you furnish on this form may be disclosed by the Office of Medicare Hearings and Appeals to another person or governmental agency only with respect to the Medicare Program and to comply with Federal laws requiring the disclosure of information or the exchange of information between the Department of Health and Human Services and other agencies.



Novocure Inc.
195 Commerce Way
Portsmouth, NH 03801

June 21, 2019

HHS OMHA Centralized Docketing
200 Public Square, Suite 1260
Cleveland, OH 44114

Dear Reviewer,

We are submitting a request for an Administrative Law Judge Hearing. Please find enclosed our completed CMS-20034 A/B form and all required supporting documentation. We have notified the patient and/or their contact that we are requesting an Administrative Law Judge Hearing for:

Beneficiary Name: David Christenson
Beneficiary Address: 5754 Clevedon Lane, Oshkosh, WI 54904
Beneficiary Medicare ID: 340483639A
Beneficiary Claim Number: 18310809384000, 18338812665000, 19007808841000
Date(s) of Service Being Appealed: 11/03/2018, 12/03/2018, 01/03/2019
Medicare Appeal Number: 1-8486340738

We are requesting the ALJ due to the fact that the reconsideration was denied as a non-covered Medicare benefit. We categorically disagree with this assertion as Optune has been classified as frequently services durable medical equipment and the coverage decision was left to "Carrier Discretion." We have included the benefit category determination from Joel Kaiser, Director of DMEPOS Policy. At the time of service, there was no NCD or LCD in effect so Novocure provided the beneficiary with the system on good faith the medical necessity of the Optune System would be easily established due to the fact that they have an inoperable brain tumor.

Additionally, there are over 100 commercial payers within the United States covering Optune therapy either on a case by case basis or through published medical policy including Aetna, Tricare, Humana, and HealthNet, to name a few.

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed review for premarket approval (PMA) for the Optune System in April 2011. As a device that has obtained FDA approval Optune should be eligible for coverage.

In addition, of great importance, is the fact that the NCCN Guidelines (National Comprehensive Cancer Network) were updated for 2015 to include TTFields treatment for recurrent glioblastoma. This recent guideline update should demonstrate the favorable outcomes of TTFields therapy using the Optune in treating patients such as Mr. Christenson.

Furthermore, multiple patients have been approved for coverage at the reconsideration level including Medicare advantage patients approved through independent external review. Medicare Region C and Region D have established precedent by considering the Optune System as a Reasonable and Necessary treatment option for specific patients. We respectfully ask that Mr. Christenson be granted the same opportunity.

Thank you for your consideration of this important request.





Sincerely,



Dan McCoy
Manager, Case Management

Enclosures

CC: Medicare Region B
Patient

| | | | |
|--------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|--------------------------------------------------------------|--|
|  UNITED STATES POSTAL SERVICE® | | www.pitneybowes.com | |
|  | US POSTAGE 06/14/2019 From 03801 | | |
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| Pitney Bowes Complete Price Flat Rate Envelope | | 026W0004897298 30000000973 | |
| PRIORITY MAIL 2-DAY™ | | | |
| Nicole Vignreau Novocure, Inc. 195 Commerce Way Portsmouth NH 03801-3251 | | | |
| Estimated Delivery Date: 06/17/2019 | | | |
| 0023 | | | |
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| HHS HHS OMHA CENTRALIZED DOCKETING 200 PUBLIC SQ, STE 1260 CLEVELAND OH 44114-2304 | | | |
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OMHA CENTRAL
JUL 01 2019 TD
OPERATION DIV.

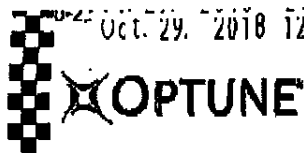
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EXHIBIT 2

Oct 29, 2018 12:36 PM FAX 5c RADIATION ONCOLOGY MMC 19202361628

No. 8869 P. 2 of 1



Optune® Prescription Form

Please fax or email signed and completed forms with medical records, face sheet, and copies of insurance card(s) to 603-501-4298 or support@novocure.com

I. PRESCRIPTION INFORMATION

| | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|---------------------------------------------------------------------------------------------------------------------------------------|--|
| Patient Name: <u>David Christenson</u> <small>(required)</small> | | Please check the appropriate box: <input type="checkbox"/> New Patient order <input checked="" type="checkbox"/> Renewal | |
| Date of Birth: <u>11/14/1953</u> <small>(required)</small> | | | |
| Is this patient enrolling in an Investigator Sponsored Trial (IST) or Cooperative Group Trial (e.g. RTOG)? <input type="checkbox"/> Yes <input type="checkbox"/> No | | If yes, which trial? _____ | |
| Optune is comprised of: an Electric Field Generator (the "Device"), Transducer Arrays (the "Arrays"), power supply items, and accessories. | | | |
| ICD-10 Code: <u>C71.9</u> <small>(required)</small> | | Diagnosis Description: <u>Recurrent GBM</u> | |
| I prescribe use of Optune, as described above, for a period of: <small>(check box required)</small> | | <input type="checkbox"/> 3 months <input checked="" type="checkbox"/> 6 months | |
| Prescriber Name (Last, First, Middle Initial): <u>Davis, Rick, D</u> <small>(required)</small> | | Name of Preferred Office Contact: <u>Same</u> | |
| NPI: <u>1861460974</u> <small>(required)</small> | | Phone: <u>920 738 2184</u> | |
| Phone: <u>920 236 1605</u> | | Phone: <u>920 236 1628</u> | |
| Fax: _____ | | Email: <u>rick.davis2@ascension.org</u> | |
| By signing and dating, I attest that I am prescribing Optune (DO NOT SUBSTITUTE) as medically necessary. I have read and understand all safety information and other instructions for use included with Optune. | | | |
| Signature: <u>[Signature]</u> <small>(required)</small> | | Date: <u>10-29-2018</u> <small>(required)</small> | |

II. ORDER INFORMATION

Treatment education, head preparation and array application will take place in the patient's home. Upon completion of the education session, the patient or caregiver may initiate treatment in the presence of Novocure personnel.

Preferred Treatment Start date (MM/DD/YYYY): _____

Please allow 5 business days from submission of all required paperwork and preferred treatment start date.

Notes

Sep. 26. 2016 1:42PM
OPTUNE

RA TION ONCOLOGY MMC

No. 0295 P. 3

Optune™ Prescription Form

Fax the completed form with signature to 603-501-4298; or Email to Support@novocure.com

III. PATIENT INFORMATION (PLEASE COMPLETE IN FULL)

| | | | |
|---------------------------------------------------------------------------------------------|------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| Permanent Address: <u>5754 CLEVELAND LANE</u> | | | |
| City: <u>OSHKOSH</u> | State: <u>WI</u> | Zip: <u>54904</u> | Phone: <u>(920) 203-5634</u> |
| Family Contact: <u>BARBARA CHRISTENSON</u> | | Phone: <u>(920) 203-5637</u> | |
| <input checked="" type="checkbox"/> Shipping and mailing address same as permanent address. | | <input type="checkbox"/> Use the address below for shipping and mailing purposes related to equipment, supplies and billing. Patient must reside at this address: | |
| Shipping and Mailing Address: _____ | | | |
| City: _____ | State: _____ | Zip: _____ | Phone: _____ |
| Primary Insurance: <u>NETWORK HEALTH</u> | | | |
| Patient ID#: <u>10541902</u> | Insurance Phone Number: <u>(920) 720-1300</u> | | |
| Group#: <u>101291</u> | Group Name: <u>STATE OF WISCONSIN</u> | | |
| Primary Insured (Subscriber) Name: <u>BARBARA J. CHRISTENSON</u> | | | |
| Relationship to Patient: <u>WIFE</u> | | Subscriber Date of Birth: <u>11-17-53</u> | |
| **If you have secondary insurance, please attach this information if applicable. | | | |

The use of "I" or "you" in this document refers to the patient named in the "Signatures" block.

Authorization to Release Records to Novocure

I authorize my physician and the practice, facility and hospital of my physician and any other holder of medical information about conditions for which I am being treated to release to Novocure Inc. and affiliated companies (together "Novocure") any information necessary for treatment, payment and healthcare operations related to my use of Optune. I authorize Novocure employees to deliver equipment and provide education in my home as well as attend my appointments as necessary to provide technical assistance to my physician and healthcare practitioners. I also authorize Novocure, my physician and the practice, facility and hospital of my physician and any other holder of medical information about conditions for which I am being treated to release such information to my insurer. These authorizations apply to my current physician and previous physicians. I understand that Novocure may and likely will use the information to seek a determination of whether my insurer will cover my use Optune.

Authorization To Discuss Care

I authorize Novocure to discuss my care with the family members and/or caregivers listed below. I may revoke this authorization at any time by calling or emailing Novocure at 855-281-9301 or support@novocure.com.

List all authorized individuals: BARBARA CHRISTENSON

Signatures: David Christenson

Patient Name (please print): DAVID P. CHRISTENSON Date: 9/22/16

If anyone other than patient completes or signs this form, please enter the following information:

Name: _____ Telephone Number: _____

Address: _____ City: _____

State: _____ Zip: _____

Relationship to Patient: _____ Reason for Signing: _____

QSF-DME-026 Rev. 02

novocure™

Page 2 of 3

this week

ASSESSMENT of NEED

| | | | |
|---------------------------------------|------------------------------------------------|-------------|--------------------------------------------------------------------------|
| Customer Name: | David Christensen | Date: | 9/27/16 |
| Customer # | 1013346 | | |
| DSS/Site | Nancy Newberg / St. Elizabeth Cancer Center | Initiation: | Home <input checked="" type="checkbox"/> Office <input type="checkbox"/> |
| Responsible Party/ Emergency Contact: | Barbara (wife) | Tel: | 920-203-5636 |

Patient acknowledges that financial responsibility has been discussed and agreed to: (Indicate date of welcome call and person spoken to)

Judi 9/27/16

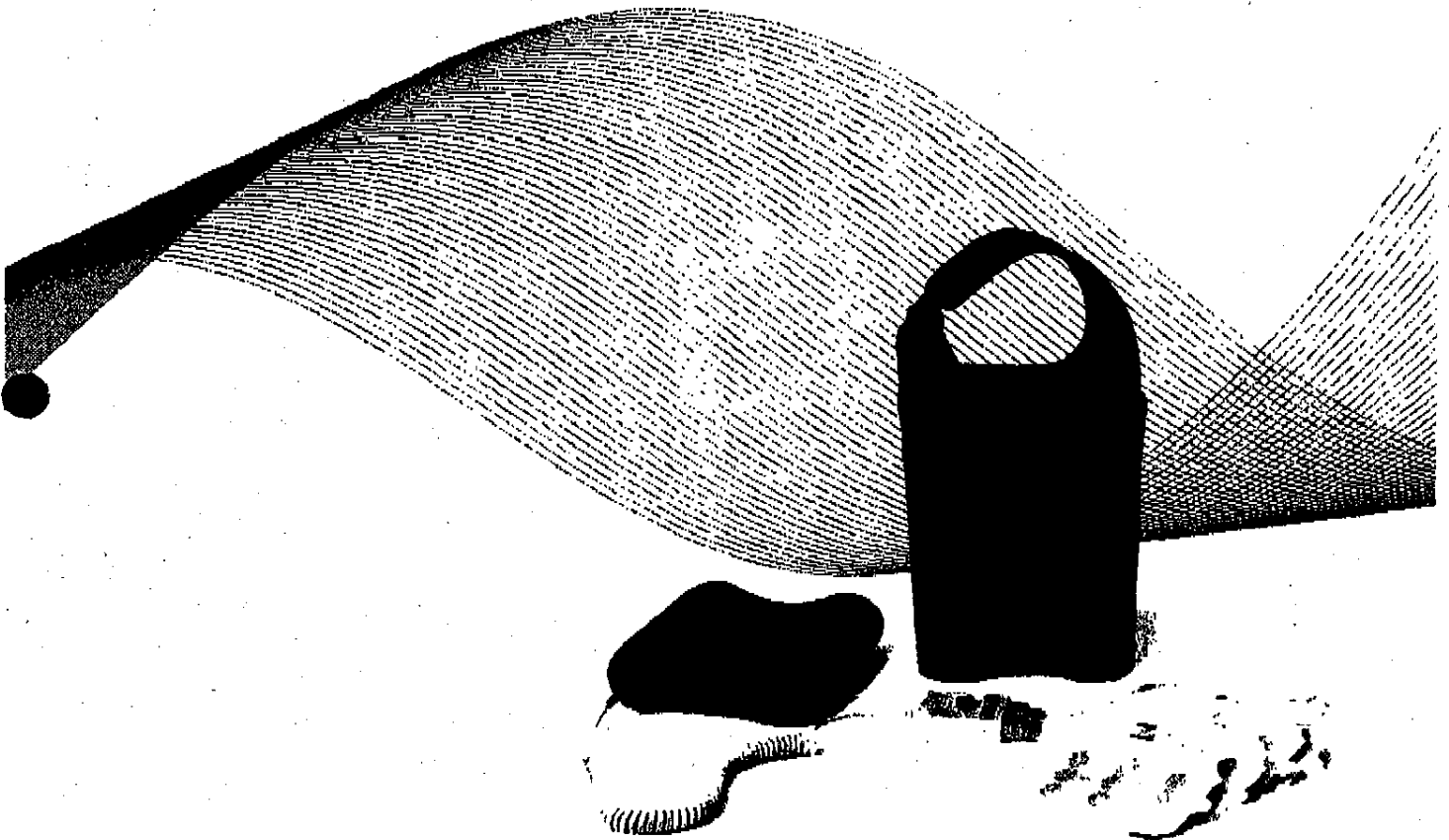
| | | | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--------------------------------------------------------------------------|--------|
| How did you hear about Optune Therapy? | | | |
| radiation oncologist | | | |
| What factors led to the decision to start treatment? | | | |
| Did you receive a package from us containing printed material and DVD? Yes No <u>Not Sure</u> | | | |
| Does patient live alone? Yes No | | Patient has access to telephone: <u>Yes</u> No | |
| Is patient residence? <u>Home</u> Assisted Living Other facility: | | | |
| In what type of structure do you reside? <u>House</u> - Apart/Condo- Assisted Living - Rehab Facility | | | |
| Where will parking be? <u>Yes</u> No <u>driveway</u> | | | |
| How will we enter / exit residence? <u>Front door</u> | | | |
| Should I be made aware of any safety concerns? ex lack of lighting, no elevator (if apt is not on 1 st floor) | | | |
| Please specify: N/A | | | |
| Are there any pets in your home? Yes <u>No</u> | | Cats # | Dogs # |
| Can pets be placed in another room while DSS present? Yes No <u>N/A</u> | | Other types # | |
| Is there smoking in the home? Yes <u>No</u> | | | |
| Is there anything that our DSS should know about the home environment or the people residing there that could be important for the safety of the visit? N/A | | | |
| Is patient able to speak: <u>Yes</u> No If yes, what is his/her primary language? <u>English</u> | | | |
| Does patient have adequate electrical capacity to utilize device and recharge batteries? <u>Yes</u> No | | | |
| Does he/she require assistance with mobility? Yes <u>No</u> | | | |
| Are you employed? Yes <u>No</u> | | If so do you plan on continuing to work? Yes <u>No</u> <u>on his own</u> | |
| If you are planning on continuing to work what is your occupation? <u>Retired</u> | | | |
| Have you discussed treatment during work hours with your employer? Yes <u>No</u> | | | |

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------|---------|
| See Technical Review Checklist: Yes - No | |
| Other: (Explain) | |
| Explain any special needs or additional training required (if applicable) N/A <input type="checkbox"/> | |
| Training on the Optune device is performed, conducted, and observed by certified physicians in accordance with FDA approval guidelines. | |
| Completed by: | Date: |
| <u>Quinn T. Miller</u> | 9/27/16 |

QSF-DME-027 Rev. 02

Printed on: 24 May 2016, 11:01:11 am; Printed by: RSULLIVAN.

David Christenson
OPTUNE® | **OPTUNE®**
SERVICE AGREEMENT



novocure

Printed on: 03 Oct 2016, 08:39:35 am; Printed by: NNEWBERG.

Supply Terms For Optune®

Background

Novocure™ Inc. is referred to as "we" or "Novocure" in this service agreement ("Service Agreement"). The use of "you" or "your" refers to the patient named in the associated Service Agreement. All capitalized terms not defined herein have the meaning defined in the Service Agreement.

Supply Terms

Optune (the "System") is comprised of two main components: (1) an Electric Field Generator (the "Device"); and (2) INE Transducer Arrays (the "Arrays") that are disposable supplies to the Device. The System also consists of power supply items and accessories.

Novocure's affiliates hold patents that cover the System, various components of the System, and using the System. Novocure hereby grants an expressly conditional license to you to use the inventions covered by those patents under the terms set forth herein. No other licenses to you are implied.

As an element of consideration for the grant of a license to you, you agree to pay Novocure a monthly fee for access to the System. Notwithstanding anything to the contrary contained in this agreement, any use of the System for which this element of consideration is absent is not licensed under the patents.

You acknowledge that, taken together, the consideration due to Novocure for access to the System reflects only the value of the "use" rights conferred by Novocure, and does not provide you with the same suite of rights that would accompany an unconditional sale. Notwithstanding anything to the contrary contained in this agreement, (1) you are not licensed to use the Device with Arrays that

were not purchased from Novocure; and (2) you are not licensed to use any given Array for more than seven (7) days.

You understand that the Device shall at all times remain the property of Novocure.

You understand and agree that Novocure has the right to inspect the System upon request and that you may be responsible for the replacement value of the System in the event it is lost, damaged, or stolen while in your possession or control.

You understand that: (i) Novocure has the option to provide new or used equipment including the Device, power supplies and accessories; (ii) you shall not modify or alter any equipment provided to you by Novocure; (iii) you will notify Novocure immediately of any equipment problems; and (iv) the equipment is only to be used upon the order and direction of your doctor.

You agree to notify Novocure if you take a break from using the System for any period of two (2) weeks or longer. In the event that the duration of a break exceeds eight (8) weeks, you agree to return the Device to Novocure and you understand that Novocure will have the option of closing your account. Thereafter, if you desire to resume using the System, you may contact your doctor and Novocure, and Novocure will review your account and work with your doctor to re-start your use of the System. At that time, Novocure may provide you another System, and you understand that you would need to sign a new Service Agreement.

You understand that the System fees will continue until the date that you call Novocure to pick up the System. You understand that Novocure may stop providing the technical support for the System and may stop providing additional Arrays or replacement items if you fail to comply with the terms of the Service Agreement and Supply Terms, including failure to pay amounts owed or to remit payments due to Novocure that you receive directly from payors.

Printed on: 03 Oct 2016, 08:39:35 am; Printed by: NNEWBERG.

Patient Care Responsibilities

You understand and acknowledge that (1) your care is under the supervision and control of your treating physician or other health care provider (e.g., nurse practitioner, physician's assistant) who is appropriately licensed, trained and authorized to prescribe and administer the System, (2) your physician or other health care provider has prescribed the System as part of your treatment and has explained to you its risks, advantages, possible complications and alternatives, and why it is considered necessary treatment for your condition, (3) Novocure's services do not include diagnostic, prescriptive, or other functions pertaining to licensed physicians or health care providers, and (4) your physician or other health care provider is solely responsible for diagnosing and prescribing drugs, equipment, and therapy for your condition and otherwise supervising and controlling your medical condition.

Financial Responsibilities

The rental fee for the System, including use of the Device, related power supplies/accessories and Arrays for 30 days is \$21,000.

Please call (855) 281-9301 if you have any questions about your financial responsibilities.

Novocure™ will review your insurance or third-party payor (together "Payor") coverage for the purposes of providing you with an estimate of your out-of-pocket costs associated with the rental fee to use the Device and the purchase of Arrays. Novocure will also prequalify you for eligibility for our Patient Assistance Programs. Formal qualification for financial assistance will require a separate application and documentation of income.

Novocure will submit a claim to your Payor for the System and may appeal such claim if denied. Novocure will bill you for your financial responsibilities related to the System when i) your Payor affirms coverage for your use of the System at the list rental fees and supply prices for

the System or ii) Novocure elects not to continue appeals of your case.

If your cost share for the System is not affordable or your Payor refuses to provide coverage for the System, you can also apply to Novocure for financial assistance.

Please contact 855-281-9301 or email support@novocure.com to inquire about financial assistance programs.

Warranty Information

Novocure will provide a replacement Device in the event of malfunction that cannot be corrected over the phone by our technical support staff. Novocure will provide replacement Arrays in the event that the Transducer Arrays are defective according to manufacturer standards. Novocure will provide replacement power supplies and accessories in accordance with the expected useful lifetime of these items. The above warranty is only valid if the System is used in accordance with the User Manual provided to you. This warranty is personal to you and non-transferable.

Lost equipment, including the Device, Arrays, power supplies and related accessories, and equipment damaged by you or your caregivers is not covered by this warranty.

Printed on: 03 Oct 2016, 08:39:35 am; Printed by: NNEWBERG.

3

Patient Information Form For Optune®

Background

Novocure™ Inc. is referred to as "Novocure" in this service agreement ("Service Agreement"). The use of "you" or "your" refers to the patient named in the associated Service Agreement. All capitalized terms not defined herein have the meaning defined in the Service Agreement.

Notice of Privacy Practices

THIS NOTICE DESCRIBES HOW HEALTH INFORMATION ABOUT YOU MAY BE USED AND DISCLOSED AND HOW YOU CAN GET ACCESS TO THIS INFORMATION. PLEASE REVIEW IT CAREFULLY.

Please contact 855-281-9301 or support@novocure.com if you have questions.

Purpose of This Notice

This notice will tell you about the ways in which Novocure may use and disclose your health information that identifies you ("PHI"). We also describe your rights and certain obligations we have regarding the use and disclosure of PHI.

Our Pledge Regarding Protected Health Information

We understand that health information about you and your health is personal. We are committed to protecting health information about you. We create a record of the products and services that we provide to you. We need this record to provide you with quality products and services used in your care and to comply with certain legal requirements. This notice applies to all of the PHI we use and disclose related to the products and services used in your care. Your personal doctor, health care provider, and other entities

providing products or services to you may have different policies or notices regarding their use and disclosure of your PHI.

Our Legal Requirements

We are required by law to:

- Make sure that health information that identifies you is kept private;
- Give you this notice of our legal duties and privacy practices with respect to PHI about you;
- Notify you if we are unable to agree to a requested restriction on how your information is used and disclosed;
- Accommodate reasonable requests that you may make to communicate PHI by alternative means or at alternative locations;
- Obtain your written authorization for purposes other than those listed below and permitted under law; and
- Follow the terms of the notice that currently is in effect.

Who Will Follow Our Privacy Practices

This notice describes Novocure's practices and that of all Novocure employees, staff, and other company personnel for US operations only.

These entities, sites, and locations follow the terms of this notice. Additionally, these entities, sites, and locations may share PHI with each for treatment, payment, or health care operations purposes described in this notice.

Printed on: 03 Oct 2016, 09:39:35 am; Printed by: NNEWBERG.

Your Rights Regarding Protected Health Information About You

You have the following rights regarding PHI we maintain about you:

Right to Inspect and Copy

You have the right to inspect and copy PHI that may be used to make decisions about your care. Usually this includes medical and billing records. To inspect and copy PHI that may be used to make decisions about you, please contact 855-281-9301 or support@novocure.com. We may charge a fee for copying requested files. We may deny your request to inspect and copy in certain circumstances. If you are denied access to PHI, you may request that the denial be reviewed. Another person chosen by us will review your request and the denial. We will comply with the outcome of that review.

Right to Amend

If you feel that PHI we have about you is incorrect or incomplete, you may ask us to amend the information. You have the right to request an amendment for as long as the information is kept by us. To request an amendment, please contact 855-281-9301 or support@novocure.com. You must provide a reason that supports your request. We may deny your request for an amendment if it does not include a reason to support that request. Additionally, we may deny your request if you ask us to amend information that:

- Was not created by us, unless the person or entity that created the information is no longer available to make the amendment;
- Is not part of the PHI kept by or for us;
- Is not part of the information which you would be permitted to inspect and copy; or
- Is accurate and complete.

Right to Accounting of Disclosures

You have the right to request an "accounting of disclosures." This accounting is a list of the disclosures we made of PHI about you. Novocure™ will provide an accounting of all but the following types of disclosure:

- Those made for treatment, payment and health care operations;
- Those made to you about your own PHI;
- Those made to persons involved in your care or other notification purposes;
- Those made pursuant to an authorization signed by you disclosing specific uses and disclosures;
- Where the disclosures are part of a Limited Data Set (as defined in the Health Insurance Portability and Accountability Act);
- Where the disclosures are incidental to an otherwise permissible disclosure;
- For national security or intelligence purposes; and
- To correctional institutions or law enforcement custodial situations.

To request this list or accounting of disclosures, please contact 855-281-9301 or support@novocure.com. We may request that you submit the request in writing. Your request must state a time period that may not be longer than six years from the date of service. Your request should indicate in what form you want the list (i.e., paper or electronic). The first list you request within a 12-month period will be free. For additional lists, we will charge you for the costs of providing the lists. We will notify you of the costs involved and you may choose to withdraw or modify your request at the time before any costs are incurred.

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Right to Request Restrictions

You have the right to request a restriction or limitation on the PHI we use or disclose about you for treatment, payment, or health care operations. You also have the right to request a limit on the PHI we disclose about you to someone who is involved in your care or the payment for your care, like a family member or friend. You may restrict disclosures of PHI to a health plan if you have paid out of pocket in full for the health care item or service. We are not required to agree to your request. If we do agree, we will comply with your request unless the information is needed to provide you emergency treatment. Please contact 855-281-9301 or support@novocure.com to request restrictions. We may request a written request. You must tell us i) what information you want to limit, ii) whether you want to limit our use, disclosure, or both, and iii) to whom you want the limits to apply, for example, disclosures to your spouse.

Right to Request Confidential Communications

You have the right to request that we communicate with you about medical matters in a certain way or at a certain location. For example, you can ask that we only contact you at work or by mail. Please contact 855-281-9301 or support@novocure.com to request confidential communications. We may request a written request. We will accommodate all reasonable requests. Your request must specify how or where you wish to be contacted.

Right to Revoke Authorization

You have the right, in those instances where written authorization is required, to revoke such authorization to use or disclose PHI except to the extent action has already been taken. Such revocation must be in writing.

Right to a Paper Copy of This Notice

You have the right to a paper copy of this notice. You may ask us to give you a copy of this notice at any time. Even if you have agreed to receive this notice electronically, you are still entitled to a paper copy of this notice. Please contact 855-281-9301 or support@novocure.com to request a paper copy.

How We May Use and Disclose Protected Health Information About You

The following categories describe different ways that we are permitted to use and disclose PHI as a health care provider. Certain of these categories may not apply to our business and we may not actually use or disclose your PHI for such purposes. Not every use or disclosure in a category will be listed. However, all of the ways we are permitted or required to use and disclose PHI, without your authorization, will fall within one of the categories.

For Treatment

We may use or disclose PHI about you to assist health care professionals and providers to provide you with medical treatment or services. For example, we may provide PHI related to your use of our products or services to your physician and the staff at your physician's practice to assist your physician in maintaining appropriate use of the device.

For Payment

We may use and disclose PHI about you so that the products and services we provide you may be billed to and payment may be collected from you, an insurance company, or a third party. For example, we may need to receive from or disclose to your health plan, Medicare, or the medical facility you resided in information about the products and services we provided to you so they or another responsible payor can pay us. This may specifically include information required for the

Prescription Order Form, Assignment of Benefits, MRIs, and medical record information. We may also tell your health care provider or plan about a product or service you are going to receive to obtain prior approval or to determine whether your provider or plan will cover that product or service.

For Marketing Purposes

At times, Novocure™, may, for the benefit of the clients, patients and market it serves, issue information, solicitations for fundraising or marketing materials on its products and services. Your rights under the Privacy rule include your ability to request restrictions or revoke the inclusion of your information at any time in all communications as well as opting into or opting out of any marketing or fundraising activities, uses and disclosures of PHI for marketing purposes, including subsidized treatment communications; disclosures that constitute a sale of PHI; and other uses and disclosures not described in this Privacy Notice or allowed by the Privacy rule.

For Health Care Operations

We may use and disclose PHI about you for our health care operations and we may use and disclose PHI about you to other health care providers involved in your care for certain health care operations they have to undertake. These uses and disclosures are necessary to run our company and make sure that users of our products receive the most cost-effective and therapeutic products possible. Examples of health care operations activities by Novocure include, but are not limited to: delivery, pick-up, and service functions; collection efforts; internal auditing; business planning (including analysis of product length of use, utility, or development/improvement of reimbursement methods or policy); assessing the quality of care and outcomes in your case and similar cases; and quality assurance/improvement activities. We may also combine PHI about many patients to decide what additional products and services we should offer, what products

and services are not needed, and to justify how effective our products are in the care of individuals such as you. We may also disclose information to medical facilities and independent researchers for review and learning purposes. We may remove information that identifies you from this set of PHI so others may use it to study health care and health care delivery without learning who the specific patients are.

Notice/Reminders

We may use and disclose PHI to contact you or arrange for your health care provider to contact you regarding product delivery, maintenance, in-service, or pick-up.

Individuals Involved in Your Care or Payment for Your Care

We may disclose to a family member, other relative, close personal friend of yours, or any other person identified by you PHI directly relevant to such person's involvement with your care or payment for your health care when you are present for, or otherwise available prior to, a disclosure and you are able to make health care decisions, if: (i) we obtain your agreement; (ii) we provide you with the opportunity to object to the disclosure and you failed to do so; or (iii) we infer from the circumstances, based upon professional judgment, that you do not object to the disclosure. We may obtain your oral agreement or disagreement to a disclosure. However, if you are not present, or the opportunity to agree or object to the disclosure cannot practicably be provided because of your incapacity or an emergency circumstance, we may, in the exercise of professional judgment, determine whether the disclosure is in your best interests, and, if so, disclose only PHI that is directly relevant to the person's involvement with your health care.

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Research

Under certain circumstances, we may use and disclose PHI about you for research purposes. For example, a research project may involve comparing the health and recovery of all patients who received a product or service for the same condition. We may also disclose PHI about you to people preparing to conduct a research project, for example to help them look for patients with specific medical circumstances. We will in most circumstances ask for your specific authorization if the researcher will have access to your name, address or other identifying information that reveals who you are.

As Required by Law

We will disclose PHI about you when required to do so by federal, state, or local law. For example, we may disclose information for judicial and administrative proceedings pursuant to legal authority; to report information related to victims of abuse, neglect or domestic violence; or to assist law enforcement officials in their law enforcement duties.

Government Functions

We may use and disclose PHI about you as required for specialized government functions such as protection of public officials, reporting to various branches of the armed services or national security activities authorized by law.

To Avert a Serious Threat to Health or Safety

We may use and disclose PHI about you when necessary to prevent a serious threat to your health and safety or the health and safety of the public or another person. Any disclosure, however, would only be to someone able to help prevent the threat.

Business Transfers

There may arise in the course of business the acquisition or sale of our business assets (Business Transfers). Such Business Transfers may involve the sale or purchase of PHI. Also, in the event that Novocure™ Inc. or its parent entity, Novocure Limited of Jersey (Channel Islands), or any subsidiary of Novocure Limited are acquired or substantially all of its assets are acquired, PHI likely will be one of the transferred assets.

Workers' Compensation

We may release PHI about you for workers' compensation or similar programs. These programs provide benefits for work-related injuries or illness.

Public Health Activities

We may use or disclose your PHI to a health oversight agency for activities authorized by law. These oversight activities include, for example, audits, investigations, inspections, and licensure. These activities are necessary for the government to monitor the health care system, government programs, and compliance with civil rights laws.

Lawsuits and Disputes

If you are involved in a lawsuit or a dispute, we may disclose PHI about you in response to a court or administrative order. We may also disclose PHI about you in response to a subpoena, discovery request, or other lawful process by someone else involved in the dispute, but only if efforts have been made to tell you about the request and obtain your written authorization or to obtain an order protecting the information requested.

Other Uses of Protected Health Information

Other uses and disclosures of PHI not covered by this notice or otherwise permitted by laws that apply to us will be made only with your written authorization. Your authorization will not be required if Novocure™ uses or discloses health information for purposes other than as covered by this notice or permitted by law if Novocure removes any information that individually identifies you before disclosing the remaining information. If you provide us authorization to use or disclose PHI about you, you may revoke that permission, in writing, at any time. If you revoke your permission, we will no longer use or disclose PHI about you for the reasons covered by your written authorization. You understand that we are unable to take back any disclosures we have already made with your permission, and that we are required to retain our records of the products and services that we provided to you.

Changes to This Notice

We reserve the right to change our information practices and to make the new provisions effective for all PHI we maintain. We also reserve the right to change this notice at any time. We reserve the right to make the revised or changed notice effective for PHI we already have about you as well as any information we receive in the future. You may request the current version of our privacy practices by contacting 855-281-9301 or support@novocure.com.

Complaints

If you believe your privacy rights have been violated, you may file a complaint with us or with the Secretary of the Department of Health and Human Services. To file a complaint with us, you must submit it in writing to Novocure. Please contact 855-281-9301 or support@novocure.com to request the current mailing instructions for Novocure.

Patient Bill of Rights

Your Rights

As a patient you have certain rights including, but not limited to, the following:

- **Information.** Patients have the right to receive accurate, easily understood information to assist them in making informed choices.
- **Choice.** Patients have the right to a choice of health care providers.
- **Access to Emergency Services.** Patients have the right to access emergency health services when and where the need arises.
- **Being a Full Partner in Health Care Decisions.** Patients have the right to participate fully in all decisions related to their health care.
- **Care Without Discrimination.** Patients have the right to considerate, respectful care from all members of the health care industry at all times and under all circumstances.
- **Privacy.** Patients have the right to communication with health care providers in confidence and to have the confidentiality of their individual identifiable health care information protected.
- **Speedy Complaint Resolution.** Patients have the right to a fair and efficient process for resolving differences.

Your Responsibilities

As a patient you have certain responsibilities including, but not limited to, the following:

- **Provide information.** You must give accurate and complete health information concerning your past illnesses, hospital stays, medications, allergies, and other pertinent items. You are also responsible for providing documentation required by your insurance company.
- **Ask questions.** You must ask questions when you do not understand medical conditions, equipment, instructions, and/or medical terminology.
- **Follow instructions.** You must adhere to your developed and updated treatment plans.
- **Accept consequences.** You must accept consequences for not following the treatment plan instructions of your doctor and nurse.
- **Understand your benefits.** You must understand what your insurance company will or will not authorize for durable medical equipment (DME) benefits.
- **Product responsibilities.** Your doctor has prescribed this medical device for the treatment and care of your disease. This is a rental device and cannot be resold. Prompt return of this device is required once therapy is completed.

- **Show respect and consideration.** You must show respect and consideration to those who are assisting you in your treatment plan, including Novocure's staff providing technical support for your use of the device.
- **Meet financial commitments.** You are responsible for any applicable co-insurance, co-payments, or private pay amounts not covered by your insurance provider.

Contact Information for Questions or Complaints

Any questions, concerns or complaints may be addressed to: 855-281-9301 (toll-free) or support@novocure.com.

You may contact the Accreditation Commission for Health Care to report any concerns or register a complaint by calling ACHC toll-free at 855-937-2242 or 919-785-1214 and request the Complaints Department.

Authorization to Release Information; Assignment of Benefits; Acknowledgment of Education and Training; Acknowledgment of Receipt of Certain Forms; and Delivery Confirmation

Background

Optune® (the "System") is comprised of two main components: (1) an Electric Field Generator (the "Device"); and (2) INE Transducer Arrays (the "Arrays") that are disposable supplies to the Device. Novocure™ Inc. is referred to as "we" or "Novocure" in this service agreement ("Service Agreement"). The use of "you" in this Service Agreement refers to the patient named in this Service Agreement.

Authorization to Release Information

You authorize your physician and the practice, facility, and hospital of your physician, and any other holder of medical information about conditions for which you are being treated to release to Novocure any information necessary for treatment, payment, and health care operations related to your use of the System. You also authorize Novocure, your physician and the practice, facility, and hospital of your physician, and any other holder of medical information about conditions for which you are being treated to release such information to your insurance company and any other entity paying for your medical care ("your payor"). These authorizations apply to your current physician and previous physicians, their practices, facilities, and hospitals.

Authorization to Discuss Care

You authorize Novocure to discuss your care with the family members and/or caregivers listed below. You may revoke this authorization at any time by calling or emailing Novocure at 855-281-9301 or support@novocure.com.

List all authorized individuals: 920-203-5637

Barb Christensen

Assignment of Benefits

You give Novocure the right to bill for and receive payments for your medical care and you direct your payor to pay Novocure directly for the System. You agree to forward all payments to Novocure in the event that your payor pays you directly, and you acknowledge that Novocure may stop supplying the

System to you if you fail to do so. You acknowledge receipt of the supply terms and information on financial responsibilities and warranties ("Supply Terms") from Novocure and agree to those terms.

Acknowledgment of Education and Training

You have received education on the use and maintenance of the System. You have been provided a technical support phone number for questions about use of the System. You have been provided with the User Manual for the System. You consent to accept phone calls from Novocure for technical support and health care operations matters, including billing matters.

Acknowledgment of Certain Forms

You acknowledge that you have received, read, and accepted all terms and conditions set forth in these documents:

1. **Patient Information Form**, which includes a Statement of Privacy Practices, Patient Bill of Rights, and Contact Information for Novocure for Questions and/or Complaints

We are required by regulation to respond to your complaints within 5 calendar days and respond back to you with the results of our investigation within 14 calendar days.

2. **Supply Terms**, which includes Financial Responsibilities and Warranty Information

3. **Advanced Beneficiary Notice** (for Medicare patients only)

The products and/or services provided to you by Novocure are subject to the supplier standards contained in the Federal regulations shown at 42 Code of Federal Regulations Section 424.57©. These standards concern business professional and operational matters (e.g., honoring warranties and hours of operation). The full text of these standards can be obtained at [http://www.palmettogba.com/Palmetto/Providers.Nsf/files/supplierstandards30.pdf/\\$File/supplierstandards30.pdf](http://www.palmettogba.com/Palmetto/Providers.Nsf/files/supplierstandards30.pdf/$File/supplierstandards30.pdf). Upon request we will furnish you a written copy of the standards.

Please sign here:

David Christensen
Signature

10/3/2016
Date

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Delivery Confirmation

You acknowledge receipt of the equipment and supplies listed below:

| Part Description | Quantity | S/N or Lot Number |
|-------------------------------------|----------|------------------------------------------------|
| Optune® Device E0766 | 1 | TFH 201213 |
| Connection Cable | 2 | CAD 202632 CAD 202717 |
| Portable Charger | 1 | ICH 200392 |
| Power Supply | 1 | SPS 201481 |
| Portable Battery | 4 | IBH 203709 IBH 203882 IBH 203716 IBH 203749 |
| Black Transducer Array (Lot#) E0766 | 20 | C1606403 |
| White Transducer Array (Lot#) E0766 | 20 | C1608902 |
| Device Combo Bag | 1 | |
| Power Cord | 2 | |
| Manual - Instructions For Use | 1 | |
| Operation Manual | 1 | |
| Self-Exchange Kit | 1 | |

You agree to the terms of this Service Agreement and of the related forms that you have received.
The authorizations granted in this Service Agreement will expire two (2) years from the date signed below.

Signatures

Patient Name (please print): David Christenson
 Patient or Authorized Signature: David Christenson Date: 10/3/2016

If anyone other than patient completes or signs this form, please enter the following information:

Name: _____ Telephone Number: _____
 Address: _____
 City, State, ZIP: _____
 Relationship to Patient: _____
 Reason for Signing: _____

For Novocure™ Use Only

Delivery Person/Service Print: Nancy Newberg
 Signature/Tracking#: Nancy Newberg
 Delivery Date: 10/3/16
 Novocure Patient ID#: 10133416
 Novocure Order #: 26585

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PATIENT INFORMATION AND CONSENT

Optune™ Treatment Education Visit

IMPORTANT: Please do not sign this consent until you read and understand the consent. Please discuss any questions you may have with the Novocure™ personnel that will conduct your treatment education. You should feel that signing this form is something you are doing voluntarily. If you feel that you are under pressure, please do not sign this form. Please read this consent to understand the purpose and nature of this treatment education visit. If you sign this consent, you confirm that you understand the purpose and nature of this visit and that you give your consent to participate in the treatment education.

You or your physician has requested that Novocure personnel conduct a treatment education visit for Optune. **If you want to hold this session at your physician's office, please tell Novocure personnel prior to the start of the session and do not sign this consent.**

You (and your caregiver(s)) are being trained regarding the use of Optune. As part of this session, you will be taught about the following:

- Use of Optune, including how to change the battery, how to recharge the battery and connect to an external power supply, how to connect the transducer arrays connectors to the connector box, and what to do when an alarm occurs;
 - How to shave your head to maintain appropriate transducer array contact with your scalp;
 - How to apply the transducer arrays to your scalp; and
 - How to turn Optune "on" and "off"
- By signing this consent, you confirm your understanding that:
- Novocure personnel conducting your treatment education session are not physicians or healthcare providers. Please talk to your

physician regarding your medical care and any questions you may have regarding your medical condition and your treatment options

- Novocure personnel are providing education regarding the use of Optune. You will also receive the Patient Instruction and Operation Manual (PIOM) for Optune, which will be a resource for any questions you may have after this session
- Novocure personnel will teach you and/or your caregiver(s) how to shave your head and apply the transducer arrays. You and/or your caregiver(s) will shave your head and apply the transducer arrays, with assistance from Novocure personnel. Novocure personnel may touch you during the session while teaching you and/or your caregiver(s) to perform these activities
 - You may suffer cuts and possible skin irritation associated with shaving your head
 - You may suffer mild to moderate skin irritation associated with application of the transducer arrays
 - You should contact your physician regarding care for any injury you suffer during this treatment education session

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- Novocure personnel will show you and/or your caregiver(s) how to begin therapy by turning Optune "on". It is your decision when to begin Optune therapy. If you initiate therapy today, please initiate therapy in the presence of Novocure personnel, who will confirm Optune is working appropriately.
- If you have a medical issue during the session, you consent to Novocure personnel calling 911 and/or emergency medical services.
- Your physician will confirm that you understand how to use Optune and its use at your next physician visit.

I agree to participate in the treatment education session described and to allow Novocure personnel to conduct the session.

By signing this form, I have not given up any of my legal rights.

Please print your name:

David Christenson

10/3/2016

(Date)

David Christenson

(Signature of Participant)

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Patient Document Acknowledgement

| <i>Document</i> | <i>Initials</i> |
|-------------------------------------------------------------------------------------|-----------------------------|
| 1. Service Agreement | <u>DC</u> |
| 2. Patient Rights and Responsibilities (From service agreement) | <u>DC</u> |
| 3. Supplier Standards (Medicare only) | <u> </u> |
| 4. Financial review/Assessment (Patient was contacted and these items discussed) | <u>DC</u> |
| 5. How to file a complaint | <u>DC</u> |

**This form is to be returned to the Commercial Operations Center along with
the signed Service Agreement.**

Technical Review of Optune®

| | |
|---------------------------------------------|---------------------------|
| Patient Name: <u>David Christenson</u> | Patient #: <u>1013346</u> |
| Patient Signature: <u>David Christenson</u> | Date: <u>10/3/2016</u> |

| |
|-----------------------------------------------------------------------------------------------------|
| Optune™ ✓ |
| <ul style="list-style-type: none"> Overview and Description Powering On/Off |

| |
|----------------------------------------------------------------------------------------------------------|
| Connection Cable ✓ |
| <ul style="list-style-type: none"> Overview and Description Connecting to Device |

| |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Powering the Device ✓ |
| <ul style="list-style-type: none"> Portable Batteries Connecting Power Sources Charging Portable Batteries Battery Charger Plug-In Power Supply |

| |
|-------------------------------------------------------------------------------|
| Carrier Bag ✓ |
| <ul style="list-style-type: none"> Placement and Carry Options |

| |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Transducer Arrays ✓ |
| <ul style="list-style-type: none"> Overview and Description Transducer Array Components Placement Recommendations How to Shift Paired Arrays at Each Array Change Skin Observation and Care Showering Disposal and Reorder |

| |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Troubleshooting ✓ |
| <ul style="list-style-type: none"> Errors Common Causes Correcting Errors nCompass™ Support Information Equipment Exchange Process |

| |
|------------------------------------------------------------------------------------------------------------------------------------------|
| Placing the Arrays ✓ |
| <ul style="list-style-type: none"> Preparing the Head Review NovoTAL Map Applying the Transducer Arrays |

| |
|-------------------------------------------------------------------------------------------------------------------------------|
| Patient Literature ✓ |
| <ul style="list-style-type: none"> Patient Information and Operation Manual Patient Quick Start Guide |

| | |
|---------------------------------------------------|----------------------|
| Novocure Employee Name: <u>Nancy Newberg</u> | Date: <u>10/3/16</u> |
| Novocure Employee Signature: <u>Nancy Newberg</u> | |

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TM-MA-002 Rev 07

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PAGE 1 of 1

ASCENSION NE WI ST. ELIZABETH HOSPITAL, APPLETON, WI
RADIATION ONCOLOGY

PATIENT NAME: CHRISTENSON, DAVID P
PROVIDER: DAVIS MD, RICK D

ADMIT DATE: 09/19/18
REPORT NO: 0922-0008

DATE OF SERVICE: 09/19/2018

FOLLOWUP NOTE FROM RADIATION ONCOLOGY CLINIC

REFERRING PHYSICIAN: Karen Gremminger, M.D.

DIAGNOSIS: Glioblastoma of the right occipital lobe. Grade is IV. Stage is not applicable. The patient's radiation therapy delivered included VMAT and IMRT to the brain on 08/17/2015, received 6000 cGy in 30 fractions, 200 cGy each, completed that on 09/28/2015. He later received a single fraction SRS within the right occipital tumor bed receiving 24 Gy in a single fraction on 01/13/2016. Currently, he is on optimum therapy. Previous visit was 06/27/2018.

INTERVAL HISTORY: The patient has had no change in his clinical status. He has no new neurologic status, no side effects. He continues to wear his Optune roughly 18 hours a day or more. They do receive updates on compliance from the Optune therapy company. An MRI of the brain done on 09/18/2018, showed stable postoperative findings. No evidence of tumor recurrence or progression. No change in T2-FLAIR signal.

REVIEWED MEDICATIONS: He is on Decadron 1 mg a day, aspirin, docusate sodium, Coumadin and acetaminophen as needed.

ALLERGIES: NO KNOWN ALLERGIES.

REVIEW OF SYSTEMS: Complete 12 system review done and intake reviewed with the patient and updated the record as needed. Pain is 0/10. Remainder of his review of systems is within normal limits. ECOG status is 0. Advanced directives completed and in place.

PHYSICAL EXAMINATION: Age appropriate male. He is wearing his Optune device on his head with associated wires and pads. Otherwise, no significant irregularities in the patient. His height is 76 inches, weight is 228 pounds. BMI is 27.8. He is appropriately counseled about this. Temperature 98.1, heart rate 56, respiratory rate is 16, blood pressure 130/60, O2 sat 97%. Brief survey of neurologic function and cranial nerves are normal. He has no abnormalities in his balance or ambulation. No further exam was performed other than noting. His mentation is excellent.

IMPRESSION: Glioblastoma in the right occipital area. The patient is post primary therapy with temozolomide and external beam radiation therapy. He had recurrence in the surgical bed roughly four months later that was treated with radiosurgery. He was then started on Optune therapy and has been stable, if not improved in his imaging since that time. He has no current concerns or problems.

CHRISTENSON, DAVID P
MRN: E000369357
ACCT: E34723117 REG CLI
DOB: 11/14/53
DEPT: E.DICT

Affinity Health System *LIVE* FCI (PCI: OE Database OSH)

1 of 2

ASCENSION NE WI ST. ELIZABETH HOSPITAL, APPLETON, WI
RADIATION ONCOLOGY

PATIENT NAME: CHRISTENSON, DAVID P

REPORT NO: 0922-0008

PLAN: He will continue on Optune therapy indefinitely. There is no data on circumstance in which this can be discontinued. He will be doing some traveling to Europe in the near future and we will have a one week break from his Optune therapy. During that period, he will reinstitute upon return. I will plan on seeing him back in 3 months with an MRI of the brain plus contrast prior to that visit. All questions were answered today.

Greater than 15 minutes, greater than 50% being counseling and coordination of care.

JOB ID: 176857

cc:

Trans: R1

Rick D. Davis, MD
Radiation Oncology
St. Elizabeth Hospital Cancer Center

Electronically Signed: RICK D DAVIS MD

10/11/18 0839

FINAL ORIGINAL IN COMPUTER PATIENT RECORD

CHRISTENSON, DAVID P

MRN: E000369357

ACCT: E34723117 REG CLI

DOB: 11/14/53

DEPT: E.DICT

Affinity Health System *LIVE* PCI (PCI: OE Database OSH)

2 of 2

DEPARTMENT OF RADIOLOGY

CHRISTENSON, DAVID P

D.O.B AGE SEX EXAM DATE
11/14/1953 64 M 09/18/18

LOC: M.RAD

Pt Ph#: 920-203-5636

MR#: 0000343818

ACCT# 003754608

Status: REG CLI

Ordered By: DAVIS MD, RICK D

| EXAM# | TYPE/EXAM | RESULT |
|-----------|------------------------|--------|
| 002857789 | MRI/HEAD W/NO CONTRAST | |

RICK D DAVIS, MD

HEAD W/NO CONTRAST

COMPARISON: MRI brain study with and without contrast dated 6/18/2018

HISTORY: Three-month follow-up.

TECHNIQUE: MRI of the brain was performed before and after intravenous administration of 10 mL of MultiHance gadolinium contrast.

FINDINGS:

BRAIN AND CSF SPACES: Postoperative findings of right craniotomy for tumor resection. Unchanged heterogeneous enhancement involving the right parietal occipital resection cavity extending to the right occipital and peritrigonal white matter. Unchanged FLAIR hyperintense signal surrounding the resection cavity and extending throughout the posterior right frontal, parietal, occipital and temporal lobes extension as well as extension into the external and internal capsules. FLAIR hyperintense signal extends across the right splenium of the corpus callosum. Unchanged FLAIR hyperintense signal in the left periventricular white matter scattered small foci of FLAIR hyperintense signal scattered throughout the white matter both cerebral hemispheres. Unchanged effacement of the right lateral ventricle. Slightly decreased effacement of the third ventricle with midline shift to the left of 4 mm. Susceptibility weighted images demonstrate hemosiderin staining associated with the resection cavity with scattered small foci in the right parietal lobe. Unchanged diffusion abnormality associated with the FLAIR hyperintense signal in the right splenium.

PITUITARY: Normal.

PINEAL: Normal.

VASCULATURE: Normal.

ORBITS: Normal.

NASAL CAVITY AND NASOPHARYNX: Normal.

PARANASAL SINUSES: There is patchy mucosal thickening of the ethmoid sinuses.

OTOMASTOID FINDINGS: Mastoid air cells are clear.

SKULL AND C-SPINE: Normal.

IMPRESSION:

PAGE 1

Signed Report Printed From PCI (CONTINUED)

DEPARTMENT OF RADIOLOGY

CHRISTENSON, DAVID P

D.O.B AGE SEX EXAM DATE
11/14/1953 64 M 09/18/18

LOC: M.RAD

Pt Ph#: 920-203-3636

MR#: 0000343818

ACCT# 003754608

Status: REG CLI

Ordered By: DAVIS MD, RICK D

| EXAM# | TYPE/EXAM | RESULT |
|-----------|------------------------|--------|
| 002857789 | MRI/HEAD W/NO CONTRAST | |

1. Stable postoperative findings of right craniotomy for right occipital tumor resection with unchanged appearance of the heterogeneously enhancing resection cavity. No evidence of tumor progression.
2. FLAIR hyperintense signal surrounding the resection cavity and extending throughout the right cerebral hemisphere as detailed above. Unchanged mass effect with 4 mm midline shift to the left.

Lisa D. Roller, MD
Division of Neuroradiology
Radiology Associates of the Fox Valley, S.C.

RAVCC
I.2

Electronically Signed By: Lisa Roller, MD
Signed Date/Time: 9/19/2018 8:11 AM

** REPORT SIGNED IN OTHER VENDOR SYSTEM 09/19/2018 **
Reported By: ROLLER, LISA MD

CC: DAVIS MD, RICK D

Edited Date: 09/19/18 by PROVIDER
Printed Date/Time: 10/29/2018 (1241)

PAGE 2

Signed Report Printed From PCI

EXHIBIT 1

June 07, 2019

**PARRISH LAW OFFICES
788 WASHINGTON RD.
PITTSBURGH, PA 15228**

Medicare Reconsideration Decision

RE:

Beneficiary: D. Christenson
Med ID#: *****QP33
Appellant: D. Christenson

Dear D. Parrish:

This letter is to inform you of the decision on your Medicare Appeal. An appeal is a new and independent review of a claim. You are receiving this letter because you requested an appeal for the services shown under the Appeal Details section.

The appeal decision is UNFAVORABLE. Our decision is that Medicare will make additional payment. More information on the decision is provided on the next pages. You are not required to take any action.

If you disagree with the decision, you may appeal to an Administrative Law Judge (ALJ). You must file your appeal, in writing, within 60 days of receipt of this letter. For more information on how to appeal, see the page entitled "Important Information About Your Appeal Rights." The amount still in dispute is estimated to be equal to over \$160.00. However, the ALJ will determine if your appeal case meets the \$160.00 amount in controversy requirement for an ALJ hearing.

If this appeal is partially favorable or unfavorable, and it originated from an overpayment, the Medicare Administrative Contractor (MAC) is responsible for processing this determination in accordance with standard Medicare methodologies. Any outstanding debts, prior coverage, and prior reimbursement will be taken into account when processing this decision. The MAC will issue a demand letter containing information regarding the collection process, interest accrual, and requesting an extended repayment schedule (ERS).

**Contact
Information**

If you have
questions, write or
call:

***C2C Innovative
Solutions, Inc.***

QIC DME
P.O. Box 44163
Jacksonville, FL
32231-4163

Telephone:
904-224-7433

Who we are:
We are a Qualified
Independent
Contractor (QIC).
Medicare has
contracted with us to
review your file and
make an independent
decision.

A copy of this letter was also sent to the parties shown below. C2C Innovative Solutions, Inc. was contracted by Medicare to review your appeal. For more information on how to appeal, see the page titled "Important Information About Your Appeal Rights."

Sincerely,



Frank A. Delli Carpini, M.D.
Medical Director

CC: D. Christenson
Novocure Inc

Summary of Facts

The service(s) shown below were submitted for payment to CGS Administrators . The explanation of the decision was released in a Medicare Summary Notice to the beneficiary and a Remittance Advice to the provider of service. A request for a Redetermination appeal was submitted to the Medicare contractor. On March 11, 2019, CGS Administrators completed the appeal, and sent notice of the decision to the appropriate parties. On April 22, 2019, we received a QIC Reconsideration request for the services referenced in the "Appeal Details" section. Information and records reviewed by the QIC in this case included:

- Refer to Explanation of Decision for Key Documents

Decision

A panel of clinical experts consisting of a physician and a licensed health care professional reviewed the claim(s).

The decision on your appeal is shown below:

| Medicare Coverage | Claim Number (ICN) | Procedure /Date of Service |
|-------------------|--------------------|------------------------------------------------|
| Non-covered | 18310809384000 | E0766: Elec Stim Cancer Treatment - (11/03/18) |
| Non-covered | 18338812665000 | E0766: Elec Stim Cancer Treatment - (12/03/18) |
| Non-covered | 19007808841000 | E0766: Elec Stim Cancer Treatment - (01/03/19) |

We have determined that the provider is responsible for the denied charges.

Explanation of the Decision

Claim Number:18310809384000

Claims for tumor treatment field therapy (TTFT) (E0766) for D. Christenson (Beneficiary or Appellant) were submitted by Novocure, Inc. (Novocure) for payment to CGS Administrators, LLC (CGS) the Durable Medical Equipment Medicare Administrative Contractor (DME MAC). The claims were denied with a finding that Medicare guidelines were not met.

On February 21, 2019, Novocure submitted a Redetermination Request to the DME MAC. On March 11, 2019, the DME MAC issued an unfavorable Redetermination Decision.

On April 22, 2019, C2C Innovative Solutions, Inc. (C2C), the DME Qualified Independent Contractor (QIC) received a Reconsideration Request dated April 16, 2019, from Debra M. Parrish, Esq. of Parrish Law Offices (also referred to as Appellant).

Key records contained in this case include:

DME MAC Redetermination Request dated February 21, 2019
DME MAC Redetermination Decision Letter dated March 11, 2019
Reconsideration Request dated April 16, 2019
Appointment of Representative (AOR) Form dated February 5, 2019
DME MAC Medical Directors Letter dated August 7, 2018
ALJ Decisions
National Comprehensive Cancer Network (NCCN) Guidelines
Centers for Medicare and Medicaid Services (CMS) Correspondence to Novocure
Clinical Studies
Food and Drug Administration Approvals
Invoice
Physician Order/Prescription
Physician Progress Notes
Diagnostic Results
Delivery Confirmation

Laws, Regulations, and Policy

For any item or service to be covered by Medicare, it must fall into a defined Medicare benefit category, it must not be statutorily excluded, it must be reasonable and necessary under § 1862(a)(1)(A) of the Social Security Act (SSA), and it must meet other Medicare program requirements for payment. Sections 414.200 through 414.232 of 42 the Code of Federal Regulations (CFR) cover payment for durable medical equipment and prosthetic and orthotic devices. The CMS Internet Only Manual (IOM), Medicare National Coverage Determinations (NCD) Manual, Publication (Pub.) 100-03, includes NCDs that pertain to certain Durable Medical Equipment, Prosthetics/Orthotics, and Supplies (DMEPOS) items. The Medicare Claims Processing Manual, Pub. 100-04, Chapter 20, instructs on billing and payment for DMEPOS. The Medicare Program Integrity Manual (PIM), Pub. 100-08, Chapter 5, provides guidance on medical review. The manuals are based upon the above cited law and regulations. DME MACs publish Local Coverage Determinations (LCDs) and related Policy Articles. The LCDs address the criteria for "reasonable and necessary," based on SSA § 1862(a)(1)(A). The articles encompass the non-medical necessity coverage and payment rules.

Reasonable and Medically Necessary

(a) Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—

(1)(A) which, except for items and services described in a succeeding subparagraph, are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member, [SSA § 1862 (a)(1)(A)]

Authority of the QIC

With regard to authority of the QIC, 42 CFR § 405.968(b) provides:

(1) National coverage determinations (NCDs), CMS Rulings, and applicable laws and regulations are binding on the QIC.

(2) QICs are not bound by LCDs, LMRPs, or CMS program guidance, such as program memoranda and manual instructions, but give substantial deference to these policies if they are applicable to a particular case. A QIC may decline to follow a policy, if the QIC determines, either at a party's request or at its own discretion, that the policy does not apply to the facts of the particular case.

(3) If a QIC declines to follow a policy in a particular case, the QIC's reconsideration explains the reasons why the policy was not followed.

(4) A QIC's decision to decline to follow a policy under this section applies only to the specific claim being reconsidered and does not have precedential effect.

(5) A QIC may raise and develop new issues that are relevant to the claims in a particular case provided that the contractor rendered a redetermination with respect to the claims. [42 CFR § 405.968(b)]

CMS Rulings

CMS Rulings are published under the authority of the Administrator of CMS. They are binding on all CMS components, on all HHS components that adjudicate matters under the jurisdiction of CMS, and on the Social Security Administration to the extent that components of the Social Security Administration adjudicate matters under the jurisdiction of CMS. [42 CFR §§ 401.108(c) and 405.1063(b)]

Definition – Contractor

Contractor means a carrier (including a Durable Medical Equipment Regional Carrier), or a fiscal intermediary (including a Regional Home Health Intermediary) that has jurisdiction for the LCD at issue. [42 CFR § 426.110]

LCD and NCD Reviews and Individual Claim Appeals

LCD and NCD reviews are distinct from the claims appeal processes set forth in part 405, subparts G and H; part 417, subpart Q; and part 422, subpart M of this chapter. [42 CFR § 426.310]

New LCD Request Requirements

Contractors [as defined in 42 CFR § 426.110] shall consider New LCD Requests to be a complete, formal request if the following are met:

- The request is in writing and can be sent to the MAC via e-mail, facsimile or written letter;
- The request clearly identifies the statutorily-defined Medicare benefit category to which the requestor believes the item or service falls under and provides a rationale justifying the assignment;
- The request shall identify the language that the requestor wants in an LCD;
- The request shall include a justification supported by peer-reviewed evidence. Full copies of published evidence to be considered shall be included and failure to include same invalidates the request;

- The request shall include information that addresses the relevance, usefulness, clinical health outcomes, or the medical benefits of the item or service; and
- The request shall include information that fully explains the design, purpose, and/or method, as appropriate, of using the item or service for which the request is made.

The MAC will review materials received within 60 calendar days upon receipt and determine whether the request is complete or incomplete. If the request is incomplete, the contractor shall respond, in writing, to the requestor explaining why the request was incomplete. If the request is complete, the MAC shall follow the process outlined in chapter 13 of Pub.100-08. A valid request response does not convey that a determination has been made whether or not the item or service will be covered or non-covered under 1862 (a)(1)(A) of the Act. The response to the requestor that the request is valid is simply an acknowledgement by the MAC of the receipt of a complete, valid request. [CMS IOM, Pub.100-08, PIM, Chapter 13, § 13.2.2.3]

LCD Reconsideration Process

The LCD reconsideration process is a mechanism by which a beneficiary or stakeholder (including a medical professional society or physician) in the MAC's jurisdiction can request a revision to an LCD. The LCD reconsideration process differs from an initial request for an LCD in that it is available only for final effective LCDs. The whole LCD or any provision of the LCD may be reconsidered. In addition, MACs have the discretion to revise or retire their LCDs at any time on their own initiative. [CMS IOM, Pub.100-08, PIM, Chapter 13, § 13.3]

Valid LCD Reconsideration Request Requirements

The requirements related to a valid LCD Reconsideration Request are as follows:

MACs shall consider all LCD reconsideration requests from:

- Beneficiaries residing or receiving care in a contractor's jurisdiction; and
- Providers doing business in a contractor's jurisdiction.
- Any interested party doing business in a contractor's jurisdiction.

MACs should only accept reconsideration requests for LCDs published as an effective final. Requests shall not be accepted for other documents including:

- National Coverage Determinations (NCDs);
- Coverage provisions in interpretive manuals;
- Proposed LCDs;
- Template LCDs, unless or until they are adopted and in effect by the contractor;
- Retired LCDs;
- Individual claim determinations

- Bulletins, articles, training materials; and
- Any instance in which no LCD exists, i.e., requests for development of an LCD.

If modification of the LCD would conflict with an NCD, the request would not be valid. The MAC should refer the requestor to the NCD reconsideration process. [CMS IOM, Pub.100-08, PIM, Chapter 13, § 13.3.2]

Reasonable and Necessary Provisions in LCDs

An item or service may be covered by a contractor LCD if:

- It is reasonable and necessary under 1862(a)(1)(A) of The Act. Only reasonable and necessary provisions are considered part of the LCD.

Reasonable and Necessary

Contractors [as defined in 42 CFR § 426.110] shall determine and describe in the LCD the circumstances under which the item or service is reasonable and necessary under 1862(a)(1)(A). Contractors shall determine if evidence exists to consider an item or service to be reasonable and necessary if the contractor determines that the service is:

- Safe and effective;
- Not experimental or investigational (exception: routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000, which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary); and
- Appropriate, including the duration and frequency that is considered appropriate for the item or service, in terms of whether it is:

Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;

Furnished in a setting appropriate to the patient's medical needs and condition;

Ordered and furnished by qualified personnel;

One that meets, but does not exceed, the patient's medical need; and

At least as beneficial as an existing and available medically appropriate alternative.
[CMS IOM, Pub.100-08, PIM, Chapter 13, § 13.5.4]

LCD L34823

LCD L34823 provides that TTFT will be denied as not reasonable and necessary. [LCD L34823 and Policy Article A52711]

Analysis

As noted above, this matter pertains to a denial of payment of claims for TTFT. Novocure disputed the denial and requested a Redetermination. The DME MAC issued an unfavorable Redetermination Decision. The DME MAC did not allow payment because the LCD states TTFT (E0766) is not reasonable and necessary. The Appellant has now requested a Reconsideration. At issue is payment for TTFT (E0766).

Please note the information obtained from the DME MAC, Novocure, and the Appellant was utilized in this Reconsideration Review. Documentation was evaluated to determine issues such as whether, in conjunction with other credible documentation, the service in question was actually provided or was provided as billed. The responsibilities of the QIC include rendering a decision only on the coverage or payment issues raised by the review request. The QIC may deny or reduce payment if it is believed the item or service at issue was not rendered or not rendered as billed. The QIC made a decision in this case based on whether the service was documented, appropriately ordered and delivered, and medically reasonable and necessary. The findings of this review are summarized below.

Appellant has set forth several arguments in the Reconsideration Request. Ms. Parrish, on behalf of the Beneficiary, opines that published literature supports the effectiveness of the device. In addition, she states the DME MAC Medical Directors have issued a statement indicating they do not interpret that the LCD applies to patients with newly diagnosed glioblastoma. Lastly, Ms. Parrish indicates the device is incorporated in the NCCN guidelines with a Category One designation.

The QIC has reviewed the correspondence Novocure received from CMS. The QIC finds the designation of an item as DME, is not an expression of coverage. In this instance, while the NovoTTF-100A System has been classified as DME, the LCD is clear in that TTFT will be denied as not reasonable and necessary.

The QIC has also reviewed the letter from the DME MAC Medical Directors and LCD L34823. Appellant interprets the August 7, 2018, letter from the DME MAC Medical Directors to indicate that the LCD does not apply to newly diagnosed glioblastoma. Review of the LCD indicates that the LCD is silent on the type of glioblastoma and does not differentiate between the newly diagnosed and recurrent glioblastoma. The LCD states that TTFT will be denied as not reasonable and necessary. The letter from the DME Medical Directors does indicate that they accepted a Reconsideration Request to consider coverage of TTFT for newly diagnosed glioblastoma. The QIC has reviewed Chapter 13 of the PIM with respect to creation of new LCDs and the Reconsideration process for changes to an existing LCD. The PIM, in pertinent part, details the following:

The development process for the new LCDs is set forth in the Medicare PIM. The CMS IOM, Pub. 100-08, PIM, Chapter 13, § 13.3 also details the process for a beneficiary or stakeholder to request a revision to an LCD, which is called the LCD Reconsideration Process. This Reconsideration Process strictly relates to potential revisions to an LCD and is separate and apart from the claims appeal process as set forth in 42 CFR § 426.310. The CMS IOM, Pub. 100-08, PIM, Chapter 13, § 13.2.2.3 states that new LCD requests will be reviewed by the MAC within 60 days of receipt of all materials and determined whether the request is complete or incomplete. If the request is incomplete, the contractor shall respond, in writing, to the requestor explaining why the request was incomplete. If the request is complete, the MAC shall follow the process outlined in Chapter 13 of the PIM. A valid request response does not convey that a determination has been made whether the item or service will be covered or non-covered under SSA § 1862 (a)(1)(A). The response to the requestor that the request is valid is simply an acknowledgement by the MAC of the receipt of a complete, valid request.

The CMS IOM, Pub. 100-08, PIM, Chapter 13, § 13.3.2 details that MACs shall consider all LCD reconsideration requests from: Beneficiaries residing or receiving care in a contractor's jurisdiction; and Providers doing business in a contractor's jurisdiction; and Any interested party doing business in a contractor's jurisdiction. MACs should only accept Reconsideration Requests for finalized LCDs that are effective and published. Requests shall not be accepted for other documents including: NCDs; Coverage provisions in interpretive manuals; Proposed LCDs; Template LCDs, unless or until they are adopted and in effect by the contractor; Retired LCDs; Individual claim determination; Bulletins, articles, training materials; and Any instance in which no LCD exists, i.e., requests for development of an LCD. If modification of the LCD would conflict with an NCD, the request would not be valid. The MAC should refer the requestor to the NCD reconsideration process. Requests shall be submitted in writing and shall identify the language that the requestor wants added to or deleted from an LCD. Requests shall include a justification supported by new evidence, which may materially affect the LCD's content or basis. Copies of published evidence shall be included. Any request for LCD reconsideration that, after MAC review, is determined to not meet these criteria is invalid. The CMS IOM, Pub. 100-08, PIM, Chapter 13, § 13.5.4 provides that an item or service may be covered by a contractor LCD if: it is reasonable and necessary under § 1862(a)(1)(A) of the SSA. Only reasonable and necessary provisions are considered part of the LCD. Contractors, as defined in 42 CFR § 426.110, shall determine and describe in the LCD the circumstances under which the item or service is reasonable and necessary under § 1862(a)(1)(A). Contractors shall determine if evidence exist to consider an item or service to be reasonable and necessary if the contractor determines that the service is: Safe and effective; Not experimental or investigational (exception: routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000, which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary); and Appropriate, including the duration and frequency that is considered appropriate for the item or service, in terms of whether it is: furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member; Furnished in a setting appropriate to the patient's medical needs and condition; Ordered and furnished by qualified personnel; One that meets, but does not exceed, the patient's medical need; and At least as beneficial as an existing and available medically appropriate alternative.

The CMS IOM, Pub. 100-08, PIM, Chapter 13, § 13.5.4 further details that Contractor LCDs shall be based on the strongest evidence available. The extent and quality of supporting evidence is key to defending challenges to LCDs. The initial action in gathering evidence to support LCDs shall always be a search of published scientific literature for any available evidence pertaining to the item or service in question. In order of preference, LCDs should be based on: Published authoritative evidence derived from definitive randomized clinical trials or other definitive studies, and general acceptance by the medical community (standard of practice), as supported by sound medical evidence based on: scientific data or research studies published in peer-reviewed medical journals; Consensus of expert medical opinion (i.e., recognized authorities in the field); or Medical opinion derived from consultations with medical associations or other health care experts.

Acceptance by individual health care providers, or even a limited group of health care providers, normally does not indicate general acceptance by the medical community. Testimonials indicating such limited acceptance, and limited case studies distributed by sponsors with financial interest in the outcome, are not sufficient evidence of general acceptance by the medical community. The broad range of available evidence must be considered and its quality shall be evaluated before a conclusion is reached.

LCDs that challenge the standard of practice in a community and specify that an item or service is never reasonable and necessary shall be based on sufficient evidence to convincingly refute evidence

presented in support of coverage.

The QIC understands that the DME MACs have found a request for reconsideration for newly diagnosed glioblastoma as valid. However, the DME MACs have not issued a new LCD providing coverage for newly diagnosed glioblastoma. The acceptance of a reconsideration request as valid by the DME MAC is not in and of itself evidence of the DME MAC's intent to allow coverage. It is merely an acknowledgement that the request for reconsideration was deemed valid, as set forth in the PIM.

According to the documentation submitted, the TTFT is being used to treat the Beneficiary's diagnosis of glioblastoma. The Appellant argues that the device is reasonable and necessary and published literature supports the effectiveness of the device. However, the QIC has reviewed the NCCN guidelines and the medical literature and finds the medical documentation of the efficacy of this device is not within the usual scope and breath of current medical literature with peer acknowledgment and review. More specifically, the QIC has reviewed the peer reviewed and evidence based literature relative to clinical trials for TTFT and found the literature and clinical trials to be limited in number and the clinical trials not non-biased; that is, the clinical trials were not independent, but funded by Novocure, Inc. The device is considered to be within the non-covered category for treatment of this condition as per the LCD.

The QIC has also reviewed LCD L34823, as noted above. The LCD for TTFT (L34823) states that for any item to be covered by Medicare, it must: 1) Be eligible for a defined Medicare benefit category; 2) Be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member; and 3) Meet all other applicable Medicare statutory and regulatory requirements. The purpose of an LCD is to provide information regarding reasonable and necessary criteria based on SSA § 1862(a)(1)(A) provisions. The LCD clearly and unequivocally states that TTFT (E0766) will be denied as not reasonable and necessary.

As noted above, the QIC understands that the DME MACs have found a request for reconsideration for newly diagnosed glioblastoma as valid. However, the DME MACs have not issued a new LCD providing coverage for newly diagnosed glioblastoma. The acceptance of a reconsideration request as valid by the DME MAC is not evidence of the DME MAC's intent to allow coverage. It is an acknowledgement that the request for reconsideration was deemed valid, as set forth in the PIM. The LCD L34823 details that TTFT (E0766) will be denied as not reasonable and necessary. This LCD remains in effect until such time the DME MAC retires the non-coverage LCD or a new LCD becomes effective. Therefore, in accordance with the aforementioned LCD, the claim for TTFT services is determined to be not reasonable or necessary.

Based on the available documentation, the requirements of the LCD and PIM have not been met. Therefore, the claims cannot receive reimbursement.

Conclusion

The decision of the QIC is unfavorable. After careful consideration, the QIC finds that the services did not meet the requirements to be considered medically reasonable and necessary in the treatment of the patients, in tandem with the application of Medicare guidelines and the Medicare Local Coverage policies.

Claim Number:18338812665000

Please refer to ICN 18310809384000 for the complete decision for this claim.

Claim Number:19007808841000

Please refer to ICN 18310809384000 for the complete decision for this claim.

Who is Responsible for the Bill?

When services are denied as not medically reasonable and necessary under the Medicare program, we must also determine if the provider or beneficiary is liable for payment. Section 1879(a)-(g) of the SSA, also referred to as "the limitation on liability provision," specifies how to arrive at this decision. Medicare regulations, 42 CFR 424, require providers to be familiar with Medicare rules and regulations. In addition, 42 CFR 411.406 provides criteria for determining when a provider is responsible for payment for the services considered not reasonable and necessary. This regulation states that providers are presumed to have knowledge of published Medicare coverage rules and regulations, Centers for Medicare and Medicaid Services (CMS) Rulings, Medicare coverage policies in CGS Administrators bulletins or websites, and acceptable standards within the local community. We find that Novocure is liable for the denied charges. The record does not support that the beneficiary was notified in advance that Medicare would likely deny payment.

Other Important Information

If you appeal this decision the Administrative Law Judge (ALJ) will not consider new evidence unless you show good cause for not presenting the evidence to the QIC. This requirement does not apply to beneficiaries, unless a provider or supplier represents the beneficiary.

For information on how to appeal this decision, refer to the page titled "Important Information About Your Appeal Rights." If you need more information or have any questions, please call 1-800-Medicare (1-800-633-4227) [TTY/TDD: 1-800-486-2048] or the phone number listed on page one.

You can receive copies of statutes, regulations, policies, and/or manual instructions we used to arrive at this decision. For instructions on how to do this, please see 'Other Important Information' on the page entitled "Important Information About Your Appeal Rights." The request must be submitted in writing to this office.

**Medicare Appeal
Number:**

1-8486340738

Appeal Details

| | | | |
|---------------------|------------------------|-----------------------------------|--------------------------------------|
| Beneficiary | D. Christenson | | |
| Provider | Novocure Inc. | | |
| Claim Number | Date of Service | Procedure | Medicare QIC Decision |
| 18310809384000 | 11/03/18 | E0766: Elec Stim Cancer Treatment | Unfavorable |
| 18338812665000 | 12/03/18 | E0766: Elec Stim Cancer Treatment | Unfavorable |
| 19007808841000 | 01/03/19 | E0766: Elec Stim Cancer Treatment | Unfavorable |

THIS IS NOT A BILL – Keep this letter or a copy for your records.

IMPORTANT INFORMATION ABOUT YOUR APPEAL RIGHTS

Your Right to Appeal this Decision

If you do not agree with this decision, you may appeal the decision to an Administrative Law Judge (ALJ) at the Office of Medicare Hearings and Appeals (OMHA). The ALJ will review the decision to determine whether it is correct.

As of January 1, 2018, you must have \$160.00 in dispute to appeal to an ALJ. A claim can be combined ("aggregated") with others to reach this amount if: (1) the other claims have also been decided or dismissed by a QIC; (2) all of the claims are listed on your request for review; (3) your request for review is filed within 60 days of receipt of all of the Qualified Independent Contractor (QIC) decisions being appealed; and (4) you explain why you believe the claims involve similar or related services.

You can find more information about your right to an ALJ review of a QIC decision at www.hhs.gov/omha or by calling 1-855-556-8475. This is a toll free call.

How to Appeal

To exercise your right to appeal, you must file a written request for an ALJ review within **60 days** of receiving this letter. If your request for review is being filed late, you must explain why your request is being filed late. After you file an appeal, you may check your appeal's status via the OMHA website at www.hhs.gov/omha (click on Appeal Status Lookup).

When preparing your request for review, please use **Form OMHA-100**, available at:

www.hhs.gov/omha/forms/index.html

If you do not use the form, your request for review must include the following:

1. The Beneficiary's name, address, and Medicare health insurance claim number;
2. The name and address of the person appealing, if the person is not the beneficiary;
3. The representative's name and address, if any;
4. The Medicare appeal number listed on the front page of this Reconsideration notice;
5. The dates of service for the claims at issue;
6. The reasons why you disagree with the QIC's decision; and
7. A statement of any additional evidence to be submitted and the date it will be submitted.

You must send a copy of the request for ALJ review to the other parties who received a copy of this decision (for example, the beneficiary or provider/supplier). Please **do not** send a copy of your review request to the QIC that issued this decision or to the Medicare Administrative Contractor (MAC) that issued the Redetermination.

Mail your review request to (tracked mail is suggested):

HHS OMHA Central Operations
200 Public Square, Suite 1260
Cleveland, OH 44114-2316

OMHA processes Medicare **Beneficiary** appeals on a priority basis. If you are a Beneficiary or you represent a Beneficiary, mail your review request to:

HHS OMHA Central Operations
Attn: Beneficiary Mail Stop
200 Public Square, Suite 1260
Cleveland, OH 44114-2316

If you are a Beneficiary or represent a Beneficiary, you can also call the OMHA Beneficiary help line at 1-844-419-3358 for assistance. This is a toll free call. For more information on the OMHA Beneficiary prioritization program, including limitations for Beneficiaries represented by a provider/supplier, or a shared representative, visit the OMHA website at www.hhs.gov/omha or call the Beneficiary help line.

Who May File an Appeal

You or someone you name to act for you (your **appointed representative**) may file an appeal. You can name a relative, friend, advocate, attorney, doctor, or someone else to act for you.

If you want someone to act for you, you and your appointed representative must sign and date a statement naming that person to act for you and send it with your request for review. Call 1-800-MEDICARE (1-800-633-4227) to learn more about how to name a representative.

Help With Your Appeal

You can have a friend or someone else help you with your appeal. If you have any questions about payment denials or appeals, you can also contact your State Health Insurance Assistance Program (SHIP). For information on contacting your local SHIP, call 1-800-MEDICARE (1-800-633-4227).

Other Important Information

If you want copies of statutes, regulations, and/or policies we used to arrive at this dismissal, please write to us and attach a copy of this letter, at:

C2C Innovative Solutions, Inc.

A Medicare Contractor
P.O. Box 44163
Jacksonville FL 32231-4163

If you have questions, please call us at the phone number provided on the front of this notice.

Other Resources To Help You

1-800-MEDICARE (1-800-633-4227),
TTY/TDD: 1-800-486-2048

If you need large print or assistance, call 1-800-633-4227

~~excludeinsert~~**Nondiscrimination Notice** - The Centers for Medicare & Medicaid Services Centers for Medicare and Medicaid Services (CMS) doesn't exclude, deny benefits to, or otherwise discriminate against any person on the basis of race, color, national origin, disability, sex, or age. If you think you've been discriminated against or treated unfairly for any of these reasons, you can file a complaint with the Department of Health and Human Services, Office for Civil Rights by:

- Calling 1-800-368-1019. TTY users should call 1-800-537-7697.
- Visiting hhs.gov/ocr/civilrights/complaints.
- Writing: Office for Civil Rights, U.S. Department of Health and Human Services, 200 Independence Avenue SW, Room 509F, HHH Building, Washington, D.C. 20201

Notice of Availability of Auxiliary Aids & Services - We're committed to making our programs, benefits, services, facilities, information, and technology accessible in accordance with Sections 504 and 508 of the Rehabilitation Act of 1973. We'll take appropriate steps to make sure that people with disabilities, including people who are deaf, hard of hearing or blind, or who have low vision or other sensory limitations, have an equal opportunity to participate in our services, activities, programs, and other benefits. We provide various auxiliary aids and services to communicate with people with disabilities, including:

- Relay service — TTY users should call 1-877-486-2048.
- Alternate formats — This Medicare Reconsideration Notice is available in alternate formats, including large print, Braille, data CD and audio CD. To request your notice in an alternate format, call 1-800-MEDICARE (1-800-633-4227). TTY users should call 1-877-486-2048.

Aviso sobre la discriminación - Los Centros de Servicios de Medicare y Medicaid (CMS) no excluye, niega beneficios o discrimina contra ninguna persona por motivos de raza, color, origen nacional, incapacidad, género o edad. Si cree que ha sido discriminado o tratado injustamente por cualquiera de estos motivos, puede presentar una queja ante el Departamento de Salud y Servicios Humanos, Oficina de Derechos Civiles:

- Llamando al 1-800-368-1019. Los usuarios de TTY deben llamar al 1-800-537-7697.
- Visitando hhs.gov/ocr/civilrights/complaints.
- Escribiendo a la: Oficina de Derechos Civiles del Departamento de Salud y Servicios Humanos 200 Independence Avenue, SW Room 509F, HHH Building Washington, D.C. 20201

Ayuda y servicios auxiliares para personas con incapacidades - Medicare está dedicado a ofrecerles a todos sus beneficiarios los programas, beneficios, servicios, dependencias, información y su tecnología, en cumplimiento con las Secciones 504 y 508 de la Ley de Rehabilitación del 1973. Medicare tomará las medidas necesarias para asegurarse de que las personas incapacitadas, entre los que se incluyen los que tiene problemas auditivos, son sordos, ciegos, tienen problemas visuales u otro tipo de limitaciones, tengan las mismas oportunidades de participar y aprovechar los programas y beneficios disponibles. Medicare ofrece varios servicios y ayuda para facilitar la comunicación con las personas incapacitadas incluyendo:

- Servicios de retransmisión de mensajes — Los usuarios de TTY deben llamar al 1-877-486-2048.
- Formatos alternativos — Los productos de Medicare, incluyendo esta reconsideración, están disponible en letra grande, versión digital, Braille y audio. Para ordenar su aviso en un formato alternativo, llame al 1-800-MEDICARE (1-800-633-4227). Los usuarios de TTY deben llamar al 1-877-486-2048.

ATTENTION: If you speak a language other than English, language assistance services, free of charge, are available to you. Call 1-800-MEDICARE (TTY: 1-877-486-2048).

ةي وغلل اةدعاسملا تامدخ ناف ،ةيزيلجنالال ريغ يرخا ةغل تشدحتت تنك ن! :عظالم ةيبرعلا (Arabic) 877-486-2048-1). (يصلل فتلال) 1-800-MEDICAREمقرلاب لصتا . ناملاب كل ةرفاوت

հայերեն (Armenian) ՈՒՇԱԴՐՈՒԹՅՈՒՆ՝ Եթե խոսում եք հայերեն, ապա ձեզ անվճար կարող են տրամադրվել լեզվական աջակցության ծառայություններ: Չանգահարեք 1-800-MEDICARE (TTY (հեռախոս)՝ 1-877-486-2048)

繁體中文 (Chinese) 注意：如果您使用繁體中文，您可以免費獲得語言援助服務。請致電 1-800-MEDICARE (TTY : 1-877-486-2048) 。

تالیهست ،دینک یم وگتفگ یسراف نابز م ربگا :هجووت (Farsi) یسراف
1-800-MEDICARE اب .دشاب یم مهارف امش یارب ناگیار تروصب ینابز
(TTY: 1-877-486-2048) دیریگب سامت.

Français (French) ATTENTION : Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 1-800-MEDICARE (ATS : 1-877-486-2048).

Kreyòl Ayisyen (French Creole) ATANSYON: Si w pale Kreyòl Ayisyen, gen sèvis èd pou lang ki disponib gratis pou ou. Rele 1-800-MEDICARE (TTY: 1-877-486-2048).

Deutsch (German) ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zur Verfügung. Rufnummer: 1-800-MEDICARE (TTY: 1-877-486-2048).

Italiano (Italian) ATTENZIONE: In caso la lingua parlata sia l'italiano, sono disponibili servizi di assistenza linguistica gratuiti. Chiamare il numero 1-800-MEDICARE (TTY: 1-877-486-2048).

日本語 (Japanese) 注意事項：日本語を話される場合、無料の言語支援をご利用いただけます。1-800-MEDICARE (TTY:1-877-486-2048) まで、お電話にてご連絡ください。

한국어(Korean) 주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다. 1-800-MEDICARE (TTY: 1-877-486-2048) 번으로 전화해 주십시오.

Polski (Polish) UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer 1-800-MEDICARE (TTY: 1-877-486-2048).

Português (Portuguese) ATENÇÃO: Se fala português, encontram-se disponíveis serviços linguísticos, grátis. Ligue para 1-800-MEDICARE (TTY: 1-877-486-2048).

Русский (Russian) ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода. Звоните 1-800-MEDICARE (телетайп: 1-877-486-2048).

Español (Spanish) ATENCIÓN: Si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 1-800-MEDICARE (TTY: 1-877-486-2048).

Tagalog (Tagalog) PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nang walang bayad. Tumawag sa 1-800-MEDICARE (TTY: 1-877-486-2048).

Tiếng Việt (Vietnamese) CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 1-800-MEDICARE (TTY: 1-877-486-2048).

May 01, 2019

**PARRISH LAW OFFICES
788 WASHINGTON RD.
PITTSBURGH, PA 15228**

RE:

Beneficiary: D. Christenson
MED ID#: *****QP33
Appellant: David Christenson

Dear D. Parrish:

This letter is to inform you that we received your reconsideration request on April 22, 2019. Medicare hired C2C Innovative Solutions, Inc. to review your appeal and make a decision.

What we do

We will look at your file carefully to make a decision. We will review Medicare rules to decide your case. If the items or service was denied as not being medically necessary, then we will ask a clinical panel to review your file.

In most cases, we will issue a decision within 60 days of your request.

What you can do

We ask that you submit any additional information you wish to have considered in your appeal to our office within 14 days. Evidence that is not submitted prior to the issuance of the reconsideration decision will not be considered at the Administrative Law Judge (ALJ) level, or made part of the administrative record, unless the appellant demonstrates good cause as to why the evidence was not provided prior to the issuance of this decision. See 42 Code of Federal Regulations (CFR) §405.966(a)(2). This requirement does not apply to beneficiaries, unless they are represented by a physician, supplier or a provider of services. Submission of all evidence will allow us to thoroughly address the issues of the case and provide an accurate determination for your appeal. Due to a rapid increase in claim appeals at

**Contact
Information**

If you have questions, write or call:

**C2C Innovative
Solutions, Inc.**

QIC DME
P.O. Box 44163
Jacksonville, FL
32231-4163

Telephone:
904-224-7433

Who we are:
We are a Qualified
Independent
Contractor (QIC).
Medicare has
contracted with us to
review your file and
make an independent
decision.

Revision date 03/21/2014

the third level of Medicare appeal; a substantial backlog has resulted that has increased the average time to decision. Our review of all pertinent supporting documentation and medical evidence will help to ensure that cases are resolved as early as possible in the appeals process.

When submitting additional documentation, please ensure the Medicare Appeals Number referenced in the upper right corner on this letter is included on all information you would like to submit and fax it to (904) 224-2760. You can also mail this information to:

QIC DME
P.O. Box 44163
Jacksonville, FL 32231-4163

You do not have to call or write to us to find out our decision. We will review your file and send you our decision.

How to get more information:

If you want a status update on your appeal, you can contact:

Beneficiaries: call 1-800-MEDICARE (1-800-633-4227)

Providers: check www.Q2A.com

For questions about your appeal other than status, please call 904-224-7433.

Sincerely,

Brian Stotler,
DME QIC-C2C Innovative Solutions, Inc.
Medicare Contractor

Appeal Details

| | |
|------------------|---------------------------|
| Appellant | David Christenson |
| ACI | CGS Administrators(17013) |

| Redetermination Number | Provider | Date of Service |
|------------------------|-----------------------|-----------------|
| 19053000193 | N/A Novocure, Inc. | 11/03/2018 |
| 19053000193 | N/A Novocure, Inc. | 12/03/2018 |
| 19053000193 | N/A Novocure, Inc. | 01/03/2019 |

THIS IS NOT A BILL – Keep this letter or a copy for your records.

PARRISH LAW OFFICES

788 WASHINGTON ROAD
PITTSBURGH, PENNSYLVANIA 15228-2021
www.dparrishlaw.com

April 16, 2019

412 561.6250
FAX 412 561.6253
E-mail info@dparrishlaw.com

VIA PRIORITY MAIL

C2C Innovative Solutions, Inc.
Attn: DME Qualified Independent Contractor (QIC)
P.O. Box 44013
Jacksonville, FL 32231-4013

Re: Request for Reconsideration
Patient: David Christenson
Medicare ID: 7QR9QM0QP33
Date of Service: 11/3/18; 12/3/18; 1/3/19
Device: E0766 KFRR (TTFT)
Supplier: Novocure, Inc.
Contractor: CGS Jurisdiction B
Our Ref: 19-296 Rec.



Dear C2C Innovative Solutions, Inc.:

On behalf of Mr. David Christenson, we hereby appeal CGS's denial of the Optune system, E0766, an FDA-approved device that treats individuals diagnosed with glioblastoma, an aggressive malignant brain cancer with few treatment options. In addition to surgery, chemotherapy, and radiation, Mr. Christenson's provider prescribed the Optune system. The contractor denied the claims, stating that "the currently published studies in the medical literature do not clearly document the effectiveness of this device." LCD L34823 is generally referenced. For the reasons outlined below, the LCD should not be deferred to for Mr. Christenson.

Contrary to the contractor's statements, the device is reasonable and necessary. The published literature supports the effectiveness of the device:

- The final analysis of the randomized phase 3 trial (695 patients) found that the addition of Optune to standard chemotherapy treatment "resulted in statistically significant improvement in progression-free survival and overall survival" over patients that were treated with chemotherapy alone. Stupp et al. at 2315 (JAMA 2017). See also, interim analysis of 315 patients from this study (adding Optune to maintenance chemotherapy "significantly prolonged progression-free and overall survival"). Stupp et al. at 2542 (JAMA 2015).

In fact, the data monitoring safety board of the EF-14 trial recommended early termination of the study to allow patients who were not receiving the device to cross over to the treatment arm and receive the Optune device, deeming it unethical to withhold it from patients in the control arm. The FDA agreed. The study included the outcomes for both newly diagnosed and recurrent

patients. The device is incorporated in the NCCN guidelines, considered the gold standard for cancer care. Based on the strength of the peer-reviewed literature and the lack of medical alternatives, the Optune system has been certified at more than 800 cancer treatment centers, and has been prescribed by over 1200 physicians in 50 states, the District of Columbia, and Puerto Rico, for over 7200 patients.

The QIC is not bound by the LCD. Prior QIC decisions have made the following bolded statements which are addressed below.

A. "The medical documentation in support of efficacy is not within the usual scope and breadth of current medical literature with peer acknowledgement and review."

Respectfully, the sentence and logic are difficult to follow. In terms of the breadth and scope of the peer-reviewed literature, a PubMed search reveals over 100 peer-reviewed articles ranging from randomized controlled trials, to case reports, to meta-analyses. The scope and breadth are particularly remarkable given the orphan status of the disease. In the past 10 years, TTFT was the only positive clinical trial and breakthrough treatment in glioblastoma. The pivotal studies were published in the Journal of the American Medical Association (JAMA), one of the most prestigious journals in the United States and one of the most cited journals in the world. Certainly, in view of the number of publications and the prestigious peer-reviewed articles that exist, it is difficult to understand the QIC's assertion that the studies do not have peer acknowledgement and review. Further, the peer-reviewed literature was and is so strong, that TTFT has been incorporated in the NCCN guidelines. Finally, based on the strength of the outcomes seen, the Data Safety Monitoring Board (DSMB) recommended early termination of the clinical trial so that those in the control arm of the clinical trial could cross over and receive treatment. This was so because it would have been unethical to withhold this life-saving treatment from the control group. Thus, the effectiveness of the treatment certainly enjoyed the "acknowledgement and review" of the DSMB and the FDA.

B. "More specifically, the QIC has reviewed the peer reviewed and evidence based literature relative to clinical trials for TTFT, and has found the literature and clinical trials to be limited in number and the clinicals trial not non-biased; that is, the clinical trials were not independent, but funded by Novocure."

Again, respectfully, the sentence and logic are difficult to follow. As noted above, GBM is an orphan disease with a difficult prognosis. More than one randomized controlled clinical trial was performed and reported in the peer-reviewed literature and more than 50 articles regarding TTFT for glioblastoma have been reported in the peer-reviewed literature. One of the seminal clinical trials resulted in multiple publications in the Journal of the American Medical Association, one of the most prestigious journals in the United States. On March 6, 2019, the Contractor Advisory Committee (CAC) recommended Medicare coverage of TTFT.¹ The experts found that the peer-reviewed literature shows the treatment is safe and effective. The experts did not find that the studies were limited in number or biased.

¹ See <https://med.noridianmedicare.com/web/jddme/policies/lcd/contractor-advisory-committee>.

PARRISH LAW OFFICES

Reconsideration Request

April 16, 2019

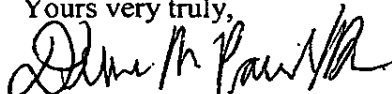
Page 3 of 4

With respect to the “not non-biased” assertion, it is unclear if the QIC is attempting to assert that the manufacturer’s funding of the clinical trials resulted in biased publications that could not support Medicare coverage. The studies were conducted at some of the most prestigious academic institutions in the United States by academic researchers. Most of the published clinical research on a medical intervention is sponsored in the United States. Indeed, Medicare often requires industry to sponsor certain studies as a condition of Medicare coverage. A cursory review of the literature supporting most LCDs shows that they are industry-sponsored studies. Industry sponsorship does not make a peer-reviewed study, written by academic authors, “not non-biased” such that the study cannot support Medicare coverage. If such a standard applied, Medicare would be precluded from considering most of the peer-reviewed literature published with respect to a technological advancement – an absurd result.

With respect to the number of clinical trials, Appellant notes that GBM is an orphan disease with a high mortality rate. Because the treatment is so effective, the FDA deemed it unethical to continue a study that withheld such an effective treatment from those battling a fatal disease. This is consistent with the Declaration of Helsinki, paragraph 18.² The CAC recognized that just as the FDA deemed it unethical to continue the clinical trial, it would be unethical to even begin more clinical studies which involved withholding a proven effective treatment for a fatal disease. A “limited number” of clinical trials is common when a treatment is proven so effective for a fatal condition. After the first study determining that a tourniquet is an effective treatment to prevent people from dying from arterial bleeding, ethically, a second study cannot be conducted. Likewise, with TTFT, given the conclusive effectiveness, additional trials that withhold the treatment cannot be conducted ethically.

Please overturn the contractor’s denial of the claims at issue given the strength of the literature, rarity of the disease, limited treatment options for patients like Mr. Christenson, and other evidence supporting the effectiveness of the device. If you have any questions regarding this reconsideration request, please do not hesitate to contact me at (412) 561-6250.

Yours very truly,



Debra M. Parrish
788 Washington Road
Pittsburgh, PA 15228

(continued on next page)

² See World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects: “When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.” The Declaration of Helsinki finds its roots in the Nuremberg Code which required informed consent for human clinical trials after the horrific experiments conducted in concentration camps during WWII. The quoted section has been interpreted to preclude continuation of a clinical trial when effectiveness has been established for a fatal illness.

PARRISH LAW OFFICES

Reconsideration Request

April 16, 2019

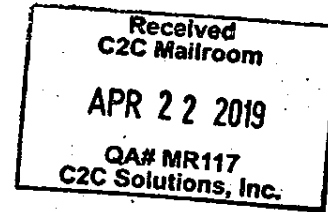
Page 4 of 4

Enclosures:

Attachment A: Appointment of Representative Form
Attachment B: CD of Supporting Documents (v.18)
Attachment C: Additional Medical Record
Attachment D: Redetermination Decision

cc: Mr. David Christenson
5754 Clevedon Ln.
Oshkosh, WI 54904

Novocure, Inc.



Hard evidence was
received with this file.

| | |
|----------|------------------|
| X | CD/DVD |
| | Thumb drive |
| | X-Ray negatives |
| | Diabetic logbook |
| | Other: |

1-2.1.01 Hard Evidence Form
09/28/2018

ATTACHMENT A
TO THE RECONSIDERATION REQUEST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR MEDICARE & MEDICAID SERVICESForm Approved
OMB No. 0938-0950

APPOINTMENT OF REPRESENTATIVE

| | |
|------------------------------------|----------------------------------------------------------------|
| NAME OF PARTY David Christenson | MEDICARE OR NATIONAL PROVIDER IDENTIFIER NUMBER 7QR9QM0QP33 |
|------------------------------------|----------------------------------------------------------------|

SECTION I: APPOINTMENT OF REPRESENTATIVE

To be completed by the party seeking representation (i.e., the Medicare beneficiary, the provider or the supplier):

I appoint this individual: Debra M. Parrish to act as my representative in connection with my claim or asserted right under Title XVIII of the Social Security Act (the "Act") and related provisions of Title XI of the Act. I authorize this individual to make any request; to present or to elicit evidence; to obtain appeals information; and to receive any notice in connection with my appeal, wholly in my stead. I understand that personal medical information related to my appeal may be disclosed to the representative indicated below.

SIGNATURE OF PARTY SEEKING REPRESENTATION:

David Christenson

DATE

1/26/2019

STREET ADDRESS

5754 Clevedon Lane

PHONE NUMBER (with Area Code)

(920) 203-5636

CITY

Oshkosh

STATE:

WI

ZIP

54904

SECTION II: ACCEPTANCE OF APPOINTMENT

To be completed by the representative:

I, Debra M. Parrish, hereby accept the above appointment. I certify that I have not been disqualified, suspended, or prohibited from practice before the Department of Health and Human Services; that I am not, as a current or former employee of the United States, disqualified from acting as the party's representative; and that I recognize that any fee may be subject to review and approval by the Secretary.

I am a/an ATTORNEY (Debra M. Parrish)

(PROFESSIONAL STATUS OR RELATIONSHIP TO THE PARTY, E.G. ATTORNEY, RELATIVE, ETC.)

SIGNATURE OF REPRESENTATIVE

[Signature]

DATE

2-5-19

STREET ADDRESS

788 Washington Road

PHONE NUMBER (with Area Code)

(412) 561-6250

CITY

Pittsburgh

STATE

PA

ZIP

15228

SECTION III: WAIVER OF FEE FOR REPRESENTATION

Instructions: This section must be completed if the representative is required to, or chooses to waive their fee for representation. (Note that providers or suppliers that are representing a beneficiary and furnished the items or services may not charge a fee for representation and must complete this section.)

I waive my right to charge and collect a fee for representing _____ before the Secretary of the Department of Health and Human Services.

SIGNATURE

DATE

SECTION IV: WAIVER OF PAYMENT FOR ITEMS OR SERVICES AT ISSUE

Instructions: Providers or suppliers serving as a representative for a beneficiary to whom they provided items or services must complete this section if the appeal involves a question of liability under section 1879(a)(2) of the Act. (Section 1879(a)(2) generally addresses whether a provider/supplier or beneficiary did not know, or could not reasonably be expected to know, that the items or services at issue would not be covered by Medicare.)

I waive my right to collect payment from the beneficiary for the items or services at issue in this appeal if a determination of liability under §1879(a)(2) of the Act is at issue.

SIGNATURE

DATE

Form CMS-1696 (10/10)

ATTACHMENT B
TO THE RECONSIDERATION REQUEST

ATTACHMENT C
TO THE RECONSIDERATION REQUEST

ASCENSION NE WI ST. ELIZABETH HOSPITAL, APPLETON, WI
RADIATION ONCOLOGYPATIENT NAME: CHRISTENSON, DAVID P
PROVIDER: DAVIS MD, RICK DADMIT DATE: 09/19/18
REPORT NO: 0922-0008

DATE OF SERVICE: 09/19/2018

FOLLOWUP NOTE FROM RADIATION ONCOLOGY CLINIC

REFERRING PHYSICIAN: Karen Gremminger, M.D.

DIAGNOSIS: Glioblastoma of the right occipital lobe. Grade is IV. Stage is not applicable. The patient's radiation therapy delivered included VMAT and IMRT to the brain on 08/17/2015, received 6000 cGy in 30 fractions, 200 cGy each, completed that on 09/28/2015. He later received a single fraction SRS within the right occipital tumor bed receiving 24 Gy in a single fraction on 01/13/2016. Currently, he is on optimum therapy. Previous visit was 06/27/2018.

INTERVAL HISTORY: The patient has had no change in his clinical status. He has no new neurologic status, no side effects. He continues to wear his Optune roughly 18 hours a day or more. They do receive updates on compliance from the Optune therapy company. An MRI of the brain done on 09/18/2018, showed stable postoperative findings. No evidence of tumor recurrence or progression. No change in T2-FLAIR signal.

REVIEWED MEDICATIONS: He is on Decadron 1 mg a day, aspirin, docusate sodium, Coumadin and acetaminophen as needed.

ALLERGIES: NO KNOWN ALLERGIES.

REVIEW OF SYSTEMS: Complete 12 system review done and intake reviewed with the patient and updated the record as needed. Pain is 0/10. Remainder of his review of systems is within normal limits. ECOG status is 0. Advanced directives completed and in place.

PHYSICAL EXAMINATION: Age appropriate male. He is wearing his Optune device on his head with associated wires and pads. Otherwise, no significant irregularities in the patient. His height is 76 inches, weight is 228 pounds. BMI is 27.8. He is appropriately counseled about this. Temperature 98.1, heart rate 56, respiratory rate is 16, blood pressure 130/60, O2 sat 97%. Brief survey of neurologic function and cranial nerves are normal. He has no abnormalities in his balance or ambulation. No further exam was performed other than noting. His mentation is excellent.

IMPRESSION: Glioblastoma in the right occipital area. The patient is post primary therapy with temozolomide and external beam radiation therapy. He had recurrence in the surgical bed roughly four months later that was treated with radiosurgery. He was then started on Optune therapy and has been stable, if not improved in his imaging since that time. He has no current concerns or problems.

CHRISTENSON, DAVID P
MRN: E000369357
ACCT: E34723117 REG CLI
DOB: 11/14/53
DEPT: E.DICT

Affinity Health System *LIVE* PCI (PCI: OE Database OSH)

1 of 2

ASCENSION NE WI ST. ELIZABETH HOSPITAL, APPLETON, WI
RADIATION ONCOLOGY

PATIENT NAME: CHRISTENSON, DAVID P

REPORT NO: 0922-0008

PLAN: He will continue on Optune therapy indefinitely. There is no data on circumstance in which this can be discontinued. He will be doing some traveling to Europe in the near future and we will have a one week break from his Optune therapy. During that period, he will reinstitute upon return. I will plan on seeing him back in 3 months with an MRI of the brain plus contrast prior to that visit. All questions were answered today.

Greater than 15 minutes, greater than 50% being counseling and coordination of care.

JOB ID: 176857

cc:

Trans: R1

Rick D. Davis, MD
Radiation Oncology
St. Elizabeth Hospital Cancer Center

Electronically Signed: RICK D DAVIS MD

10/11/18 0839

FINAL ORIGINAL IN COMPUTER PATIENT RECORD

CHRISTENSON, DAVID P

MRN: E000369357

ACCT: E34723117 REG CLI

DOB: 11/14/53

DEPT: E.DICT

Affinity Health System *LIVE* PCI (PCI: OE Database OSH)

2 of 2

DEPARTMENT OF RADIOLOGY

CHRISTENSON, DAVID P

D.O.B AGE SEX EXAM DATE
11/14/1953 64 M 09/18/18
LOC: M.RAD
Pt Ph#: 920-203-5636
MR#: 0000343818
ACCT# 003754608
Status: REG CLI

Ordered By: DAVIS MD, RICK D

| EXAM# | TYPE/EXAM | RESULT |
|-----------|------------------------|--------|
| 002857789 | MRI/HEAD W/WO CONTRAST | |

RICK D DAVIS, MD

HEAD W/WO CONTRAST

COMPARISON: MRI brain study with and without contrast dated 6/18/2018

HISTORY: Three-month follow-up.

TECHNIQUE: MRI of the brain was performed before and after intravenous administration of 10 mL of MultiHance gadolinium contrast.

FINDINGS:

BRAIN AND CSF SPACES: Postoperative findings of right craniotomy for tumor resection. Unchanged heterogeneous enhancement involving the right parietal occipital resection cavity extending to the right occipital and peritrigonal white matter. Unchanged FLAIR hyperintense signal surrounding the resection cavity and extending throughout the posterior right frontal, parietal, occipital and temporal lobes extension as well as extension into the external and internal capsules. FLAIR hyperintense signal extends across the right splenium of the corpus callosum. Unchanged FLAIR hyperintense signal in the left periventricular white matter scattered small foci of FLAIR hyperintense signal scattered throughout the white matter both cerebral hemispheres. Unchanged effacement of the right lateral ventricle. Slightly decreased effacement of the third ventricle with midline shift to the left of 4 mm. Susceptibility weighted images demonstrate hemosiderin staining associated with the resection cavity with scattered small foci in the right parietal lobe. Unchanged diffusion abnormality associated with the FLAIR hyperintense signal in the right splenium.

PITUITARY: Normal.

PINEAL: Normal.

VASCULATURE: Normal.

ORBITS: Normal.

NASAL CAVITY AND NASOPHARYNX: Normal.

PARANASAL SINUSES: There is patchy mucosal thickening of the ethmoid sinuses.

OTOMASTOID FINDINGS: Mastoid air cells are clear.

SKULL AND C-SPINE: Normal.

IMPRESSION:

PAGE 1

Signed Report Printed From PCI (CONTINUED)

DEPARTMENT OF RADIOLOGY

CHRISTENSON, DAVID P

D.O.B AGE SEX EXAM DATE
11/14/1953 64 M 09/18/18

LOC: M.RAD

Pt Ph#: 920-203-5636

MR#: 0000343818

ACCT# 003754608

Status: REG CLI

Ordered By: DAVIS MD, RICK D

| EXAM# | TYPE/EXAM | RESULT |
|-----------|------------------------|--------|
| 002857789 | MRI/HEAD W/NO CONTRAST | |

1. Stable postoperative findings of right craniotomy for right occipital tumor resection with unchanged appearance of the heterogeneously enhancing resection cavity. No evidence of tumor progression.
2. FLAIR hyperintense signal surrounding the resection cavity and extending throughout the right cerebral hemisphere as detailed above. Unchanged mass effect with 4 mm midline shift to the left.

Lisa D. Roller, MD
Division of Neuroradiology
Radiology Associates of the Fox Valley, S.C.

RAFVCC
I.2

Electronically Signed By: Lisa Roller, MD
Signed Date/Time: 9/19/2018 8:11 AM

** REPORT SIGNED IN OTHER VENDOR SYSTEM 09/19/2018 **
Reported By: ROLLER, LISA MD

CC: DAVIS MD, RICK D

Edited Date: 09/19/18 by PROVIDER
Printed Date/Time: 10/29/2018 (1241)

PAGE 2

Signed Report Printed From PCI

ATTACHMENT D
TO THE RECONSIDERATION REQUEST

CGS
Jurisdiction B
P.O. BOX 20007
Nashville, TN 37202

MEDICARE DME



March 11, 2019

7-7-19

NOVOCURE INC
195 COMMERCE WAY
PORTSMOUTH NH 03801

Beneficiary Name: David Christenson
Medicare ID: XXXXXXXXQP33
Appeal Number: 19053000193
Date(s) of Service: November 3, 2018, December 3, 2018 and January 3, 2019
Claim Control Number (CCN): 18310809384000, 18338812665000 and 19007808841000
Type of Service: Tumor Treatment Field Therapy (TTFT)
Supplier: NOVOCURE INC

Dear NOVOCURE INC:

Please note that if you did not request this appeal, you are receiving this letter as a copy.

DECISION

This letter is to inform you of an **UNFAVORABLE** Medicare Appeal decision. Based on a new and independent review of the claims at issue, we find the **ELECTRICAL STIMULATION DEVICE USED FOR CANCER TREATMENT, INCLUDES ALL ACCESSORIES, ANY TYPE (E0766)** is not covered by Medicare. The beneficiary is not responsible for payment. If you disagree with this decision, you may appeal to the Qualified Independent Contractor (QIC), C2C Solutions, Inc., as explained in the Future Appeal Rights section of this letter.

SUMMARY OF FACTS

Claims were submitted for the **ELECTRICAL STIMULATION DEVICE USED FOR CANCER TREATMENT, INCLUDES ALL ACCESSORIES, ANY TYPE (E0766)** for dates of service November 3, 2018, December 3, 2018 and January 3, 2019. The claims were initially denied on November 12, 2018, because Medicare guidelines were not met. A redetermination request was received on February 22, 2019. The redetermination case included the following documentation: medical records, administrative records and order.

APPLICABLE MEDICARE GUIDELINES AND RULES

The Medicare coverage policies are set forth below for the item or service in question. These rules are available at www.cgsmedicare.com.

19053000193

6723630001

CGS
Jurisdiction B
P.O. BOX 20007
Nashville, TN 37202

MEDICARE DME



- CMS Medicare Coverage Database, Local Coverage Determination (LCD)-L34823-Tumor Treatment Field Therapy (TTFT)
- Social Security Act, Section 1879, Limitation on Liability

EXPLANATION OF THE DECISION

The CMS Medicare Coverage Database, Local Coverage Determination (LCD)-L34823-Tumor Treatment Field Therapy (TTFT) states that for any item to be covered by Medicare the items or services must: 1) be eligible for a defined Medicare benefit category, 2) be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member, and 3) meet all other applicable Medicare statutory and regulatory requirements. It is expected that the beneficiary's medical records will reflect the need for the care provided. The beneficiary's medical records include the physician's office records, hospital records, nursing home records, home health agency records, records from other healthcare professionals and test reports. This documentation must be available upon request. Our review finds the following criteria have not been met:

- Tumor treatment field therapy (E0766) or therapy supplies (A4555) are not covered by Medicare as the currently published studies in the medical literature do not clearly document the effectiveness of this device. (LCD L34823-Tumor Treatment Field Therapy (TTFT), Coverage Indications, Limitations, and/or Medical Necessity)

A review of the documentation submitted with the redetermination request has been completed. Due to the Medicare guidelines discussed above, a favorable decision cannot be made at this time.

WHO IS RESPONSIBLE FOR THE BILL

After determining that the item or service will not be covered by Medicare, we must determine who is financially liable for the denied item or service. When an item or service is denied under §1862(a)(1), §1862(a)(9), or §1879(g) of the Social Security Act (the Act), we must determine if the beneficiary and the provider or supplier either knew or could reasonably be expected to know that the item or service would not be covered. This is known as the limitation on liability provision of §1879 of the Act.

If the beneficiary was informed by their provider or supplier in writing in advance of receiving the item/service that Medicare may not make payment (through receipt of an Advance Beneficiary Notice of Noncoverage (ABN)), the beneficiary may be responsible for the cost of the denied item or service. If the provider or supplier knew or could reasonably be expected to know the item or service would not be covered, but the beneficiary did not have such knowledge, then the provider or supplier may be responsible for the cost of the denied item or service.

In addition, we have determined that the supplier either knew or could reasonably be expected to know that the service/item would not be covered. After reviewing the claims, we have determined that the services were not reasonable and necessary. We have also determined the beneficiary could not have been expected to know these services were non-covered. Prior to furnishing this service you did not obtain a valid signed Advance Beneficiary Notice of Noncoverage notifying the beneficiary that Medicare may not pay. Based on the information contained in the CMS Medicare Coverage Database, Local Coverage Determination (LCD)-L34823-Tumor Treatment

19053000193

6723630001

CGS
Jurisdiction B
P.O. BOX 20007
Nashville, TN 37202

MEDICARE DME

Field Therapy (TTFT), you could have been expected to know these services were non-covered. Therefore, you are liable for full charges for the services.

You may not bill the beneficiary for the cost of the denied item or service, and must refund any monies collected from the beneficiary.

Beneficiaries who have incurred a charge for this service may be due a refund. In order to receive reimbursement, the beneficiary must submit the following to this office: (1) a copy of this notice, (2) the supplier's invoice, and (3) a receipt or other documents indicating the beneficiary has made payment.

FUTURE APPEAL RIGHTS

If you disagree with this decision, you must request a reconsideration, in writing, within 180 days of receiving this letter. Your reconsideration request must include a copy of this letter along with the beneficiary's name, Medicare number, item or service in question, date of service, name of person appealing, signature, and date of signature. You may request an appeal by using the form enclosed with this letter. A copy of the reconsideration request form is also located at <http://www.cgsmedicare.com/jb/index.html> or at www.C2Cinc.com. Reconsideration requests must be mailed to:

C2C Solutions, Inc.
Attn: DME Qualified Independent Contractor (QIC)
P. O. Box 44013
Jacksonville, FL 32231-4013

All evidence should be submitted with the reconsideration request. As explained in the Explanation of Decision section above, your reconsideration request should include documentation that shows the tumor treatment field therapy (E0766) is covered by Medicare and records that show the currently published studies in the medical literature does document the effectiveness of this device. All evidence must be presented before the reconsideration decision is issued. You will not be allowed to submit any new evidence to the Administrative Law Judge or the Medicare Appeals Council unless you can demonstrate good cause for not submitting the evidence to the QIC during the reconsideration process.

NOTE: You do not need to resubmit documentation that was submitted as part of the redetermination. This information will be forwarded to the QIC as part of the case file utilized in the reconsideration process.

If you need more information or have any questions, please visit our Web site at <http://www.cgsmedicare.com/jb/index.html> or call 1-866-590-6727.

Sincerely,

CGS, DME MAC Jurisdiction B
Medicare Appeals Department

cc: David Christenson

19053000193

6723630001

MEDICARE DME Redetermination Request Form

Supplier Information

Supplier Name Novocure INCPTAN 6723630001 NPI 1255617569Tax ID 205063536Address 195 Commerce WayCity PortsmouthState NH Zip Code 03801Phone Number (603) 617-4768

Jurisdiction A - Noridian Healthcare Solutions

☒ Jurisdiction B - CGS

Jurisdiction C - CGS

Jurisdiction D - Noridian Healthcare Solutions

Beneficiary Information

Patient Name David ChristensonMedicare Number 7QR9QM0QP33State WisconsinPhone Number (920)203-5636Requestor's Name/Supplier Contact Name Todd GlynnRequestor's Signature (required) Todd GlynnDate 2-21-2019

Overpayment Appeal ☐ Yes If yes, who requested overpayment: ☐ Medical Review ☐ ZPIC/PSC
☐ CERT ☐ Recovery Auditor

| Date of Service | HCPCS & Modifiers | CCN | Date of Initial Determination |
|-----------------|-------------------|----------------|-------------------------------|
| 11/03/2018 | E0766 KF RR | 18310809384000 | 11/12/2018 |
| 12/03/2018 | E0766 KF RR | 18338812665000 | 12/10/2018 |
| 1/03/2019 | E0766 KF RR | 19007808841000 | 01/11/2019 |
| | | | |
| | | | |
| | | | |

Suggested Documentation Check List: ☒ Medicare Remittance Advice ☒ CMN/DIF/Physician's Written Order
☐ ABN ☒ Medical Documentation

Reasons/Rationale - The submission of this redetermination is in regards to the denial code received: (CO-50)-"These are non-covered services because this is not deemed a 'medical necessity' by the payer." Novocure has been FDA approved since April 2011. Please see attached documentation for review.

Fax Numbers

Noridian Healthcare Solutions - JA 1-701-277-7856
 CGS Administrators, LLC - JB 1-615-660-5976
 CGS Administrators, LLC - JC 1-815-782-4630
 Noridian Healthcare Solutions - JD 1-701-277-7886



Page 1 of 1
 April 12, 2016.
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David P. Christenson
5754 Clevedon Lane
Oshkosh, WI 54904

October 11, 2018

Attn: Medicare Appeals
Re: Denial of My Cancer Treatment
Policy#: 340483639A

To whom it may concern:

This letter is in response to Medicare denial of my physician's prior authorization request for coverage of Tumor Treatment Fields therapy (TTF) using Optune for my recurrent glioblastoma.

I am submitting this letter as an urgent member grievance so that I may obtain approval of my badly needed, FDA APPROVED, treatment for my cancer.

According to the letter we received from Medicare, the request for coverage for services was denied based upon the following reason: "Experimental".

First of all, I have to strongly disagree with this rationale. This treatment has been approved by the **United States Food and Drug Administration** for treatment of glioblastoma. Furthermore, my physician feels that this treatment is my best hope for slowing down the progression of my disease. I find it unconscionable that Medicare is second guessing the treatment decisions of my physician, Dr. Rick Davis, who is one of the country's leading experts on this treatment.

TTF is my **best option** to treat this fatal disease. I have submitted the attached clinical information from my physicians as well as peer reviewed literature to assist you in considering approval of this treatment.

This procedure has been covered by many local and national insurance companies including: Humana Medicare Advantage, AARP Medicare Advantage and Aetna Medicare Advantage. This is only a representative sampling of payers covering Optune for this cancer indicating that there is enough "proven" evidence to warrant coverage for Optune in treating glioblastoma. **I am demanding that my clinical situation be reviewed by a board certified physician specializing in neuro-oncology or neurosurgery who has specific expertise in treating patients with glioblastoma with TTF.**

I am a 65 year old gentleman being treated for glioblastoma. I have been married for 41 years. I have two children, 36 and 33 years old, and two grandchildren ages 6 and 3. I am currently not working (retired). I did work part-time prior to my disease. I worked in the information technology field doing software development for 30+ years. After retirement, I worked part-time driving for a company whose clients were primarily veterans. I transported veterans to their medical appointments. I retired after 25 years for one company. I subsequently worked 6 years for the transportation company. In my free time, I enjoy biking, golfing, traveling and listening to audio books.

Initially, I had experienced headaches for several weeks. When they worsened and included vomiting, I went to urgent care and then to the hospital emergency room. I had emergency surgery the following day. I was on chemotherapy and radiation for 6 weeks after surgery. Subsequently, I was on a chemotherapy regimen of 5 days a week for one year. I experienced profound fatigue during and for some time after the chemotherapy and radiation treatment phases. I currently experience some fatigue, but to a much lesser degree. With Optune I have virtually no side effects aside from mild fatigue.

After discussing treatment options with Dr. Rick Davis, my doctor decided to prescribe Optune. Given the aggressive nature, and extremely limited treatment options of my disease, my doctor recommended I receive coverage for Optune, as it is the best FDA approved option at this time for treating my recurrent glioblastoma. I began utilizing TTFIELDS on 10/03/2016.

I believe Optune is preventing the development of new tumor cells, which I understand is its purpose. I am currently 3 years beyond my GBM diagnosis and I am considered to be a long-term survivor. I attribute this to Optune. My initial prognosis was extremely grim. Optune has provided a non-invasive treatment that allows me to live a fairly normal life. At the same time, my MRI results have consistently indicated that this treatment is working, giving my family and me reason to be optimistic and hopeful for the future.

Please note that the NCCN Guidelines (National Comprehensive Cancer Network) were updated for 2015 to include TTFIELDS treatment for recurrent glioblastoma as a category 2B recommendation.

I am aware that my cancer is considered an "orphan disease," due to the rarity of people who get glioblastoma. Despite these interventions I have received to date, TTF therapy is my best hope to control my brain tumor.

I cannot emphasize enough the urgency and importance of this matter.

Should you have any additional questions regarding my condition or the proposed treatment, please feel free to contact me at (920)-203-5636.

I also give consent for Novocure to work on the appeal on my behalf.

Thank you for your timely consideration and hopeful approval of this case.

Sincerely,

David P Christenson

David P. Christenson

Attachments

| Change Healthcare ERA Check 1 of 1 | | EFT/Check #: 09183160041 | EFT/Check Date: 11/12/2018 | EFT/Check Amount: \$.00 | Payment Type: NON | | | | | |
|-----------------------------------------------------------------|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|-----------|-----------|---------------------|---------|
| | | Payer Name: CGS - DME MAC JURISDICTION B | | CH Payer Id: MR031 | CH Process Date: 11/13/2018 | | | | | |
| | | Provider Name: NOVOCURE INC | Tax Id: 205063536 | NPI: 1255617569 | Other Payee Id: | | | | | |
| | | Address: 195 COMMERCE WAY, PORTSMOUTH NH 038019999 | | Addl. Payee Id: 1255617569 | Total PLB Adj Amt: 21000 | | | | | |
| Service Dates: 11/03/2018 | | Processing Status: 4 - Denied | | | | | | | | |
| Payer Claim # / Medicare ICN #: 18310809384000 | | CH Claim Trace Id: 309334771250657 | Place Of Service: | Total Adjustment Amount: \$.00 | | | | | | |
| Charge: \$ 21,000.00 | | Paid: \$.00 | Patient Responsibility: \$ - | Deductible: \$ - | | | | | | |
| Co-Insurance: \$ - | | Co-Pay: \$ - | Other/Crossover Insurance: | | | | | | | |
| Remark Codes: | N793 | Alert: CMS is changing from the Medicare Health Insurance Claim number (HICN) to the new Medicare Beneficiary Identifier (MBI). You can use either the HICN or MBI during the transition period. Visit www.cms.gov/newcard for important dates and information about this change. Start: 07/01/2017 Last Modified: 11/01/2017 Notes: (Modified 11/1/2017) | | | | | | | | |
| | MA13 | Alert: You may be subject to penalties if you bill the patient for amounts not reported with the PR (patient responsibility) group code. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 4/1/07) | | | | | | | | |
| | MA01 | Alert: If you do not agree with what we approved for these services, you may appeal our decision. To make sure that we are fair to you, we require another individual that did not process your initial claim to conduct the appeal. However, in order to be eligible for an appeal, you must write to us within 120 days of the date you received this notice, unless you have a good reason for being late. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 10/31/02, 6/30/03, 8/1/05, 4/1/07) | | | | | | | | |
| | M25 | The information furnished does not substantiate the need for this level of service. If you believe the service should have been fully covered as billed, or if you did not know and could not reasonably have been expected to know that we would not pay for this level of service, or if you notified the patient in writing in advance that we would not pay for this level of service and he/she agreed in writing to pay, ask us to review your claim within 120 days of the date of this notice. If you do not request an appeal, we will, upon application from the patient, reimburse him/her for the amount you have collected from him/her in excess of any deductible and coinsurance amounts. We will recover the reimbursement from you as an overpayment. Start: 01/01/1997 Last Modified: 11/01/2010 Notes: (Modified 10/1/02, 6/30/03, 8/1/05, 11/5/07, 11/1/10) | | | | | | | | |
| | N115 | This decision was based on a Local Coverage Determination (LCD). An LCD provides a guide to assist in determining whether a particular item or service is covered. A copy of this policy is available at www.cms.gov/mcd , or if you do not have web access, you may contact the contractor to request a copy of the LCD. Start: 05/30/2002 Last Modified: 07/01/2010 Notes: (Modified 4/1/04, 7/1/10) | | | | | | | | |
| PATIENT - SUBSCRIBER INFORMATION | | | | | | | | | | |
| Patient Name: CHRISTENSON, DAVID | | Patient Id: 7GRQGM0QP33 | | Patient Control Number: 0001013346 | | | | | | |
| Corrected Patient/Subscriber Name: | | | | Corrected Patient/Subscriber Member ID: | | | | | | |
| Subscriber Name: | | Subscriber Id: | | Group/Policy Id: | | | | | | |
| Other Subscr. Name: | | Other Subscriber Id: | | Group/Policy Id: | | | | | | |
| REMITTANCE PROCESSING INFORMATION - SERVICE LINE DETAIL | | | | | | | | | | |
| Svc Line # | Service Date | Proc Code - Units Modifiers | Charge \$ | Allowed \$ | Not Allowed \$ | Deductible \$ | Co-Ins \$ | Co-Pay \$ | Late Filing Red. \$ | Paid \$ |
| 1 | 11/03/2018 | E0756 - 0 KF, RR | 21,000.00 | .00 | .00 | - | - | - | - | - |
| SUPPLEMENTAL INFORMATION/ADJUSTMENT INFORMATION - SERVICE LINES | | | | | | | | | | |
| Svc Line # | Core Business Scenario | Supp/Adj Group Code | Description | Supp/Adj Reason Code | Description | Amount \$ | | | | |
| 1 | 3 | CO | Contractual Obligations | 50 | These are non-covered services because this is not deemed a 'medical necessity' by the payer. Usage: Refer to the 835 Healthcare Policy Identification Segment (loop 2110 Service Payment Information REF), if present. Start: 01/01/1995 Last Modified: 07/01/2017 | 21,000.00 | | | | |
| Claim 1 of 1 | | | Page 1 of 1 | | | | | | | |

| Change Healthcare ERA Check 1 of 1 | | EFT/Check #: 09183440058 | EFT/Check Date: 12/10/2018 | EFT/Check Amount: \$.00 | Payment Type: NON | | | | | | |
|-----------------------------------------------------------------|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|-----------|-----------|---------------------|---------|--|
| | | Payer Name: CGS - DME MAC JURISDICTION B | | CH Payer Id: MR031 | CH Process Date: 12/11/2018 | | | | | | |
| | | Provider Name: NOVOCURE INC | Tax Id: 205063534 | NPI: 1255617569 | Other Payee Id: | | | | | | |
| | | Address: 195 COMMERCE WAY, PORTSMOUTH NH 038019999 | | Addl. Payee Id: 1255617569 | Total PLB Adj Amt: 21000 | | | | | | |
| Service Dates: 12/03/2018 | | Processing Status: 4 - Denied | | | | | | | | | |
| Payer Claim # / Medicare ICN #: 18338812665000 | | CH Claim Trace Id: 337347979056658 | Place Of Service: | Total Adjustment Amount: \$.00 | | | | | | | |
| Charge: \$ 21,000.00 | | Paid: \$.00 | Patient Responsibility: \$ - | Deductible: \$ - | | | | | | | |
| Co-Insurance: \$ - | | Co-Pay: \$ - | Other/Crossover Insurance: | | | | | | | | |
| Remark Codes: | N793 | Alert: CMS is changing from the Medicare Health Insurance Claim number (HICN) to the new Medicare Beneficiary Identifier (MBI). You can use either the HICN or MBI during the transition period. Visit www.cms.gov/newcard for important dates and information about this change. Start: 07/01/2017 Last Modified: 11/01/2017 Notes: (Modified 11/1/2017) | | | | | | | | | |
| | MA13 | Alert: You may be subject to penalties if you bill the patient for amounts not reported with the PR (patient responsibility) group code. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 4/1/07) | | | | | | | | | |
| | MA01 | Alert: If you do not agree with what we approved for these services, you may appeal our decision. To make sure that we are fair to you, we require another individual that did not process your initial claim to conduct the appeal. However, in order to be eligible for an appeal, you must write to us within 120 days of the date you received this notice, unless you have a good reason for being late. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 10/31/02, 6/30/03, 8/1/05, 4/1/07) | | | | | | | | | |
| | M25 | The information furnished does not substantiate the need for this level of service. If you believe the service should have been fully covered as billed, or if you did not know and could not reasonably have been expected to know that we would not pay for this level of service, or if you notified the patient in writing in advance that we would not pay for this level of service and he/she agreed in writing to pay, ask us to review your claim within 120 days of the date of this notice. If you do not request an appeal, we will, upon application from the patient, reimburse him/her for the amount you have collected from him/her in excess of any deductible and coinsurance amounts. We will recover the reimbursement from you as an overpayment. Start: 01/01/1997 Last Modified: 11/01/2010 Notes: (Modified 10/1/02, 6/30/03, 8/1/05, 11/5/07, 11/1/10) | | | | | | | | | |
| | N115 | This decision was based on a Local Coverage Determination (LCD). An LCD provides a guide to assist in determining whether a particular item or service is covered. A copy of this policy is available at www.cms.gov/mac , or if you do not have web access, you may contact the contractor to request a copy of the LCD. Start: 05/30/2002 Last Modified: 07/01/2010 Notes: (Modified 4/1/04, 7/1/10) | | | | | | | | | |
| PATIENT - SUBSCRIBER INFORMATION | | | | | | | | | | | |
| Patient Name: CHRISTENSON, DAVID | | Patient Id: 7QR9QM0QP33 | | Patient Control Number: 0001013346 | | | | | | | |
| Corrected Patient/Subscriber Name: | | | | Corrected Patient/Subscriber Member ID: | | | | | | | |
| Subscriber Name: | | Subscriber Id: | | Group/Policy Id: | | | | | | | |
| Other Subscr. Name: | | Other Subscriber Id: | | Group/Policy Id: | | | | | | | |
| REMITTANCE PROCESSING INFORMATION - SERVICE LINE DETAIL | | | | | | | | | | | |
| Svc Line # | Service Date | Proc Code - Units Modifiers | Charge \$ | Allowed \$ | Not Allowed \$ | Deductible \$ | Co-Ins \$ | Co-Pay \$ | Late Filing Red. \$ | Paid \$ | |
| 1 | 12/03/2018 | E0766 - 0 KF, RR | 21,000.00 | .00 | .00 | - | - | - | - | - | |
| SUPPLEMENTAL INFORMATION/ADJUSTMENT INFORMATION - SERVICE LINES | | | | | | | | | | | |
| Svc Line # | Core Business Scenario | Supp/Adj Group Code | Description | Supp/Adj Reason Code | Description | Amount \$ | | | | | |
| 1 | 3 | CO | Contractual Obligations | 50 | These are non-covered services because this is not deemed a 'medical necessity' by the payer. Usage: Refer to the 835 Healthcare Policy Identification Segment (loop 2110 Service Payment Information REF). If present. Start: 01/01/1995 Last Modified: 07/01/2017 | 21,000.00 | | | | | |
| Claim 1 of 1 | | | | | | Page 1 of 1 | | | | | |

| Change Healthcare ERA Check 1 of 1 | | EFT/Check #: 09190110009 | EFT/Check Date: 01/11/2019 | EFT/Check Amount: \$.00 | Payment Type: NON | | | | | | |
|-----------------------------------------------------------------|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|-----------|-----------|---------------------|---------|--|
| | | Payer Name: CGS - DME MAC JURISDICTION B | | CH Payer Id: MR031 | CH Process Date: 01/14/2019 | | | | | | |
| | | Provider Name: NOVOCURE INC | Tax Id. 205063536 | NPI: 1255617569 | Other Payee Id: | | | | | | |
| | | Address: 195 COMMERCE WAY, PORTSMOUTH NH 038019999 | | Addl. Payee Id: 1255617569 | Total PLB Adj Amt: 21000 | | | | | | |
| Service Dates: 01/03/2019 | | Processing Status: 4 - Denied | | | | | | | | | |
| Payer Claim # / Medicare ICN #: 19007808841000 | | CH Claim Trace Id: 004362849314658 | Place Of Service: | Total Adjustment Amount: \$.00 | | | | | | | |
| Charge: \$ 21,000.00 | | Paid: \$.00 | Patient Responsibility: \$ - | Deductible: \$ - | | | | | | | |
| Co-Insurance: \$ - | | Co-Pay: \$ - | Other/Crossover Insurance: | | | | | | | | |
| Remark Codes: | N793 | Alert: CMS is changing from the Medicare Health Insurance Claim number (HICN) to the new Medicare Beneficiary Identifier (MBI). You can use either the HICN or MBI during the transition period. Visit www.cms.gov/newcard for important dates and information about this change. Start: 07/01/2017 Last Modified: 11/01/2017 Notes: (Modified 11/1/2017) | | | | | | | | | |
| | MA13 | Alert: You may be subject to penalties if you bill the patient for amounts not reported with the PR (patient responsibility) group code. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 4/1/07) | | | | | | | | | |
| | MA01 | Alert: If you do not agree with what we approved for these services, you may appeal our decision. To make sure that we are fair to you, we require another individual that did not process your initial claim to conduct the appeal. However, in order to be eligible for an appeal, you must write to us within 120 days of the date you received this notice, unless you have a good reason for being late. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 10/31/02, 6/30/03, 8/1/05, 4/1/07) | | | | | | | | | |
| | M25 | The information furnished does not substantiate the need for this level of service. If you believe the service should have been fully covered as billed, or if you did not know and could not reasonably have been expected to know that we would not pay for this level of service, or if you notified the patient in writing in advance that we would not pay for this level of service and he/she agreed in writing to pay, ask us to review your claim within 120 days of the date of this notice. If you do not request an appeal, we will, upon application from the patient, reimburse him/her for the amount you have collected from him/her in excess of any deductible and coinsurance amounts. We will recover the reimbursement from you as an overpayment. Start: 01/01/1997 Last Modified: 11/01/2010 Notes: (Modified 10/1/02, 6/30/03, 8/1/05, 11/5/07, 11/1/10) | | | | | | | | | |
| | N116 | This decision was based on a Local Coverage Determination (LCD). An LCD provides a guide to assist in determining whether a particular item or service is covered. A copy of this policy is available at www.cms.gov/lcd , or if you do not have web access, you may contact the contractor to request a copy of the LCD. Start: 05/30/2002 Last Modified: 07/01/2010 Notes: (Modified 4/1/04, 7/1/10) | | | | | | | | | |
| PATIENT - SUBSCRIBER INFORMATION | | | | | | | | | | | |
| Patient Name: CHRISTENSON, DAVID | | Patient Id: 7GR9QM0QP33 | | Patient Control Number: 0001013346 | | | | | | | |
| Corrected Patient/Subscriber Name: | | | | Corrected Patient/Subscriber Member ID: | | | | | | | |
| Subscriber Name: | | Subscriber Id: | | Group/Policy Id: | | | | | | | |
| Other Subscr. Name: | | Other Subscriber Id: | | Group/Policy Id: | | | | | | | |
| REMITTANCE PROCESSING INFORMATION - SERVICE LINE DETAIL | | | | | | | | | | | |
| Svc Line # | Service Date | Proc Code - Units Modifiers | Charge \$ | Allowed \$ | Not Allowed \$ | Deductible \$ | Co-Ins \$ | Co-Pay \$ | Late Filing Red. \$ | Paid \$ | |
| 1 | 01/03/2019 | E0766 - 0 KF, RR | 21,000.00 | .00 | .00 | - | - | - | - | - | |
| SUPPLEMENTAL INFORMATION/ADJUSTMENT INFORMATION - SERVICE LINES | | | | | | | | | | | |
| Svc Line # | Core Business Scenario | Supp/Adj Group Code | Description | Supp/Adj Reason Code | Description | Amount \$ | | | | | |
| 1 | 3 | CO | Contractual Obligations | 50 | These are non-covered services because this is not deemed a 'medical necessity' by the payer. Usage: Refer to the 835 Healthcare Policy Identification Segment (loop 2110 Service Payment Information REF), if present. Start: 01/01/1995 Last Modified: 07/01/2017 | 21,000.00 | | | | | |
| Claim 1 of 1 | | | Page 1 of 1 | | | | | | | | |

novocure

Invoice

Novocure Inc.
195 Commerce Way
Portsmouth, NH 03801

DATE: DECEMBER 03, 2018
INVOICE # [111]

Bill To:
David Christenson
5754 Clevedon Lane
OshKosh, WI 54904

Ship To:
David Christenson
5754 Clevedon Lane
OshKosh, WI 54904

Ordered By: Rick Davis, MD

| ITEM # | DESCRIPTION | QTY | UNIT PRICE | LINE TOTAL |
|-----------|-----------------------------------|-----|------------|-----------------------|
| TFH9000 | NOVO-TTF 100A PLUS TRANSDUCERS | 1 | \$21,000 | \$21,000 |
| SUBTOTAL | | | | \$21,000 |
| SALES TAX | | | | 0 |
| TOTAL | | | | \$21,000 Per Month |

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OshKosh, WI 54904

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5754 Clevedon Lane
OshKosh, WI 54904

Ordered By: Rick Davis, MD

| ITEM # | DESCRIPTION | QTY | UNIT PRICE | LINE TOTAL |
|-----------|-----------------------------------|-----|------------|-----------------------|
| TFH9000 | NOVO-TTF 100A PLUS TRANSDUCERS | 1 | \$21,000 | \$21,000 |
| SUBTOTAL | | | | \$21,000 |
| SALES TAX | | | | 0 |
| TOTAL | | | | \$21,000 Per Month |

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L11449 Surgical Dressings

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L11525 Therapeutic Shoes for Persons with Diabetes

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L11526 Tracheostomy Care Supplies

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L28616 Transcutaneous Electrical Joint Stimulation Devices (TEJSD)

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L5031 Transcutaneous Electrical Nerve Stimulators (TENS)

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L34665 Tumor Treatment Field Therapy (TTFT)

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L11566 Urological Supplies

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L34675 Vacuum Erection Devices (VED)

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Version 1.2018

March 20, 2018

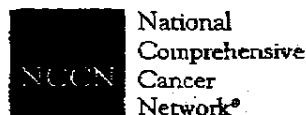
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Central Nervous System Cancers

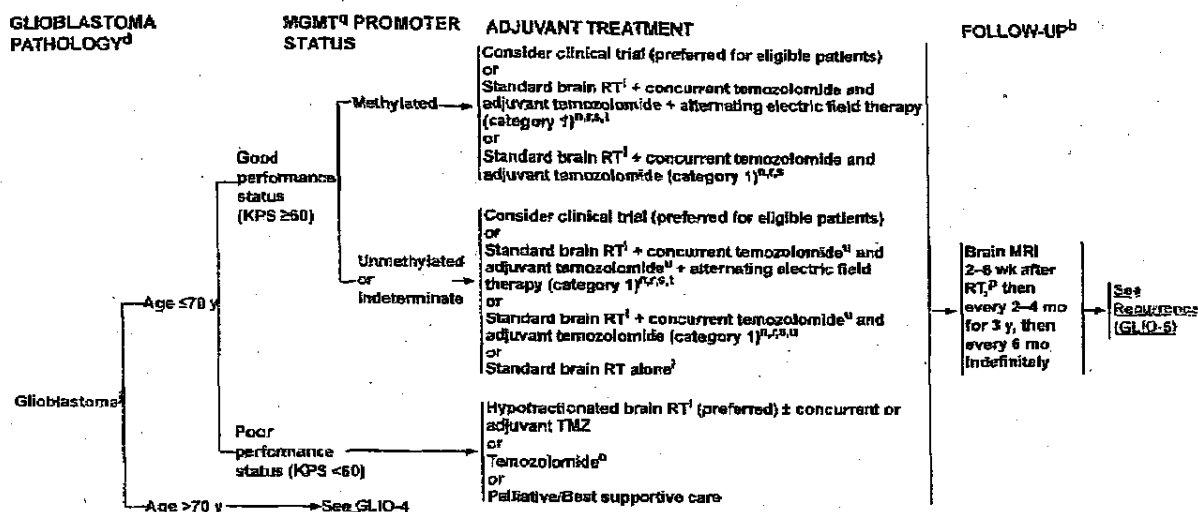
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Anaplastic Gliomas^a/Glioblastoma



^aThis pathway includes the classification of mixed AOA, AA, AO, and other rare anaplastic gliomas.

^bSee Principles of Brain and Spinal Cord Tumor Imaging (BRIN-1).

^cSee Principles of Brain Tumor Pathology (BRIN-2).

^dThis pathway also includes gliosarcoma.

^eSee Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRIN-3).

^fSee Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRIN-4).

^gConsider temozolomide if tumor is MGMT promoter methylated.

^hWithin the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.

ⁱMGMT = O⁶-methylguanine-DNA methyltransferase.

^jCombination of agents may lead to increased toxicity or radiographic changes.

^kBenefit of treatment with temozolomide for glioblastomas beyond 6 months is unknown.

^lAlternating electric field therapy is only an option for patients with supratentorial disease.

^mClinical benefit from temozolomide is likely to be lower in patients whose tumors lack

MGMT promoter methylation.

All recommendations are category 2A unless otherwise indicated.

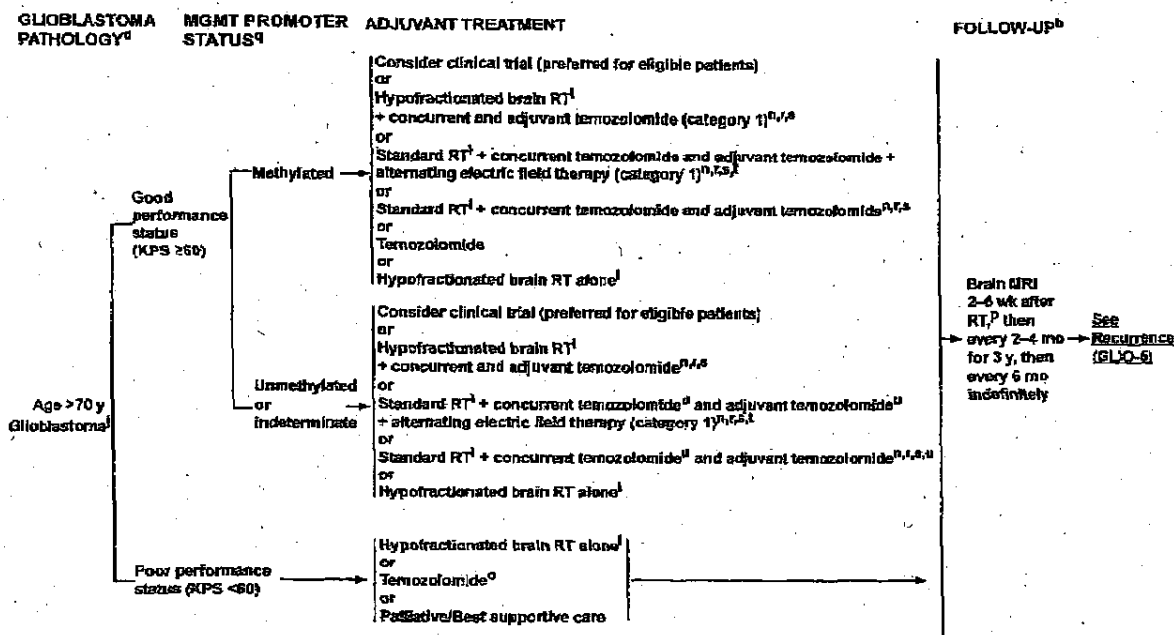
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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GLIO-3

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Anaplastic Gliomas^a/Glioblastoma



See footnotes on GLIO-4A

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GLIO-4

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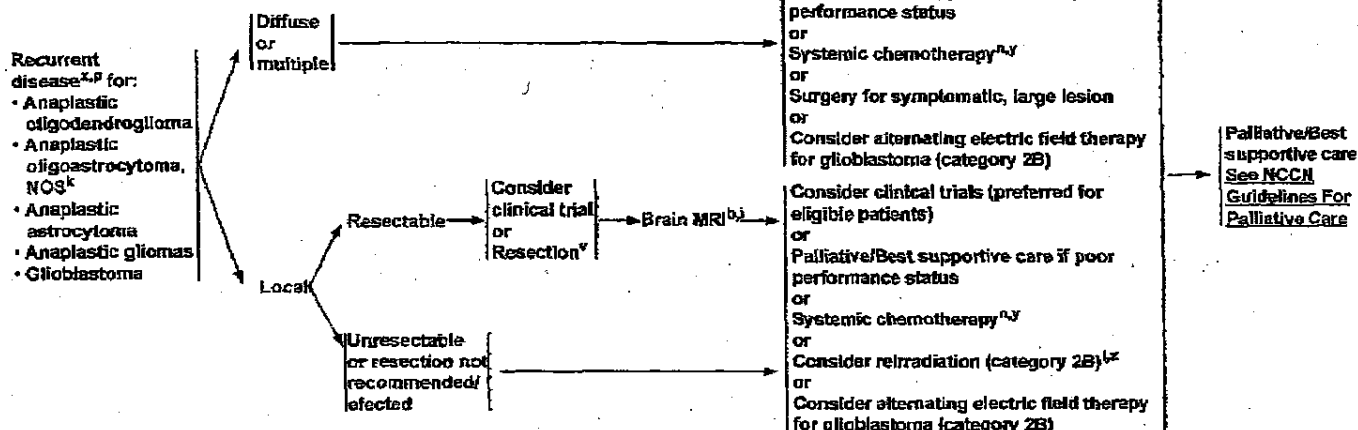
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NCCN Guidelines Version 1.2018 Anaplastic Gliomas^a/Glioblastoma

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[Discussion](#)

RECURRENCE

TREATMENT^W



^aThis pathway includes the classification of mixed AOA, AA, AO, and other rare anaplastic gliomas.

^bSee Principles of Brain and Spine Tumor Imaging (BRIN-A).

^cPostoperative brain MRI within 24–72 hours after surgery.

^dThe 2016 WHO Classification of Tumors of the CNS has deleted oligoastrocytoma as a category, although "anaplastic oligoastrocytoma, NOS" may continue to be used for 1) patients with mixed histology and no available molecular data (ie, no tissue available for analysis) for determining whether to classify as oligodendroglioma versus astrocytoma; or 2) rare instances in which the tumor has regions with histologic features of oligoastrocytoma with 1p19q-codeletion, and distinct regions with histologic features of astrocytoma without 1p19q-codeletion.

^eSee Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRIN-C).

^fSee Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRIN-D).

^WWithin the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.

^XConsider carmustine (BCNU) water implant during resection. Treatment with carmustine water may impact enrollment in clinical trials.

^YThe efficacy of standard-of-care treatment for recurrent glioblastoma is suboptimal, so for eligible patients consideration of clinical trials is highly encouraged. Prior treatment may impact enrollment in clinical trials.

^ZConsider biopsy, MR spectroscopy, MR perfusion, brain PET/CT, or brain PET/MRI, or re-image to follow changes that may be due to progression versus radionecrosis.

^UAnaplastic oligodendrogliomas have been reported to be especially sensitive to chemotherapy. Chemotherapy using temozolomide or nitrosourea-based regimens may be appropriate.

^VEspecially if long interval since prior RT and/or if there was a good response to prior RT.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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GLIO-6

Research

JAMA Oncology | Original Investigation

Influence of Treatment With Tumor-Treating Fields on Health-Related Quality of Life of Patients With Newly Diagnosed Glioblastoma

A Secondary Analysis of a Randomized Clinical Trial

Martin J. B. Taphoorn, MD; Linda Dirven, PhD; Andrew A. Kanner, MD; Giti Lavy-Shahaf, PhD; Uri Weinberg, MD, PhD; Sophie Taillibert, MD; Steven A. Toms, MD; Jerome Honnorat, MD, PhD; Thomas C. Chen, MD, PhD; Jan Sroubek, MD; Carlos David, MD; Ahmed Idraih, MD, PhD; Jacob C. Easaw, MD, PhD; Chae-Yong Kim, MD, PhD; Jordi Bruna, MD, PhD; Andreas F. Hottinger, MD, PhD; Yvonne Kew, MD, PhD; Patrick Roth, MD; Rajiv Desai, MD; John L. Villano, MD, PhD; Elon D. Krison, MD, PhD; Zvi Ram, MD; Roger Stupp, MD

 Invited Commentary

 Supplemental content

IMPORTANCE Tumor-treating fields (TTFields) therapy improves both progression-free and overall survival in patients with glioblastoma. There is a need to assess the influence of TTFields on patients' health-related quality of life (HRQoL).

OBJECTIVE To examine the association of TTFields therapy with progression-free survival and HRQoL among patients with glioblastoma.

DESIGN, SETTING, AND PARTICIPANTS This secondary analysis of EF-14, a phase 3 randomized clinical trial, compares TTFields and temozolomide or temozolomide alone in 695 patients with glioblastoma after completion of radiochemotherapy. Patients with glioblastoma were randomized 2:1 to combined treatment with TTFields and temozolomide or temozolomide alone. The study was conducted from July 2009 until November 2014, and patients were followed up through December 2016.

INTERVENTIONS Temozolomide, 150 to 200 mg/m²/d, was given for 5 days during each 28-day cycle. TTFields were delivered continuously via 4 transducer arrays placed on the shaved scalp of patients and were connected to a portable medical device.

MAIN OUTCOMES AND MEASURES Primary study end point was progression-free survival; HRQoL was a predefined secondary end point, measured with questionnaires at baseline and every 3 months thereafter. Mean changes from baseline scores were evaluated, as well as scores over time. Deterioration-free survival and time to deterioration were assessed for each of 9 prespecified scales and items.

RESULTS Of the 695 patients in the study, 639 (91.9%) completed the baseline HRQoL questionnaire. Of these patients, 437 (68.4%) were men; mean (SD) age, 54.8 (11.5) years. Health-related quality of life did not differ significantly between treatment arms except for itchy skin. Deterioration-free survival was significantly longer with TTFields for global health (4.8 vs 3.3 months; $P < .01$); physical (5.1 vs 3.7 months; $P < .01$) and emotional functioning (5.3 vs 3.9 months; $P < .01$); pain (5.6 vs 3.6 months; $P < .01$); and leg weakness (5.6 vs 3.9 months; $P < .01$), likely related to improved progression-free survival. Time to deterioration, reflecting the influence of treatment, did not differ significantly except for itchy skin (TTFields worse; 8.2 vs 14.4 months; $P < .001$) and pain (TTFields improved; 13.4 vs 12.1 months; $P < .01$). Role, social, and physical functioning were not affected by TTFields.

CONCLUSIONS AND RELEVANCE The addition of TTFields to standard treatment with temozolomide for patients with glioblastoma results in improved survival without a negative influence on HRQoL except for more itchy skin, an expected consequence from the transducer arrays.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00916409

JAMA Oncol. doi:10.1001/jamaoncol.2017.5082
Published online February 1, 2018.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Martin J. B. Taphoorn, MD, PhD, Department of Neurology, Haaglanden Medical Center, PO BOX 2191, 2501 VC, The Hague, The Netherlands (m.taphoorn@haaglandenmc.nl).

Glioblastoma has a poor prognosis,^{1,2} and, as tumors grow, patients often experience a progressive decline in neurologic function and health-related quality of life (HRQoL).³⁻⁷ The current standard of care is not curative but results in prolongation of life. However, extension of survival is meaningful only if patients' functioning and well-being can be retained or improved.⁸⁻¹¹ Therefore, it is important to determine the net clinical benefit of each new treatment or treatment modality introduced; possible benefits of a new treatment, in terms of prolonged survival, have to be carefully weighed against potential negative effects of the treatment on the patients' quality of life.

The current standard of care for patients with newly diagnosed glioblastoma comprises surgical resection to the extent safely feasible followed by radiotherapy with concomitant and maintenance chemotherapy with temozolomide.¹² Tumor-treating fields (TTFields) (Optune; Novocure Ltd) is an antimitotic physical treatment modality^{13,14} delivered by a home use medical device with wired transducer arrays placed on the patients' scalp. When added to standard maintenance temozolomide chemotherapy, TTFields has been demonstrated to improve both progression-free survival and overall survival in a randomized clinical trial (NCT00916409).¹⁵

Treatment with TTFields involves the patient carrying a mobile electrical device for more than 18 hours per day and having 4 arrays of transducers continuously fixed to the shaved scalp. Concerns regarding the influence of wearing the device on patients' HRQoL have therefore been raised.^{15,17} The incidence of adverse events was not increased by the addition of TTFields to temozolomide therapy except for an expected mild to moderate skin irritation beneath the electrodes in 52% of patients (severe in 2%). Herein, we report on the influence of treatment with TTFields on the patients' HRQoL, which was a predefined secondary objective of the randomized clinical trial. The present study was conducted from July 2009 until November 2014, and patients were followed up through December 2016.

Methods

Study Population

Patients eligible for this study were aged 18 years or older, had newly diagnosed and histologically confirmed supratentorial glioblastoma (World Health Organization grade IV astrocytoma), were progression free after undergoing maximal safe debulking surgery or biopsy, and had completed standard radiotherapy with concomitant temozolomide. Patients were required to have a Karnofsky Performance Status score of at least 70 at the time of enrollment, corresponding to at least being able to perform self-care. Further details on the study population are available elsewhere.¹⁵ All patients provided written informed consent, and the study was approved by the institutional review boards or ethics committees of all participating centers and the relevant competent authorities (eAppendix 1 in Supplement 1); the participants did not receive financial compensation.

Key Points

Question What is the influence of adding tumor-treating fields to the standard treatment on health-related quality of life in patients with glioblastoma?

Findings In this secondary analysis of the EF-14 randomized clinical trial, the addition of tumor-treating fields did not negatively influence health-related quality of life except for itchy skin, an expected consequence from the transducer arrays.

Meaning Tumor-treating field therapy has previously been shown to prolong both progression-free and overall survival. When considering the net clinical benefit, improved survival without a negative influence on health-related quality of life supports the addition of tumor-treating fields to standard treatment in patients with glioblastoma.

Study Design and Treatment

This prospective, multicenter, open-label, randomized clinical phase 3 trial recruited 695 patients at 90 medical centers in North America, Europe, the Republic of Korea, and Israel. The trial protocol is available in Supplement 2. The trial was designed to test the efficacy of TTFields in combination with the best standard of care in the treatment of newly diagnosed glioblastoma (ie, radiotherapy with concomitant and adjuvant temozolomide). The primary end point was progression-free survival, with overall survival as a powered secondary end point. Health-related quality of life was a secondary end point. Patients who were progression free after completion of radiochemotherapy were randomized within 4 to 7 weeks at a ratio of 2:1 to receive standard maintenance temozolomide chemotherapy (150-200 mg/m² for 5 days every 28 days for 6 cycles) with or without the addition of TTFields, if tolerated well, TTField therapy was to be continued until the second progression or up to 2 years.

Patients in the TTFields plus temozolomide group received continuous TTFields combined with maintenance temozolomide. TTFields were delivered through a portable device in an outpatient setting. Patients receiving TTFields had 4 transducer arrays with 9 insulated electrodes each placed on the shaved scalp and connected to a portable device set to generate 200-kHz electric fields within the brain. Although uninterrupted treatment was recommended, the patient could take short breaks if needed; patients were advised to continue treatment for at least 18 hours a day. More details on the study design and treatment are published elsewhere.¹⁵

HRQoL Assessment

The evaluation of HRQoL was performed using the validated European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ-C30) and brain module (QLQ-BN20).¹⁸⁻²⁰ Questionnaires were completed on paper at baseline (prior to randomization) and subsequently every 3 months for up to 12 months. Nine scales and items were prespecified as important based on relevance for patients with glioblastoma and hypothesized effects of the TTFields delivery device on patients' HRQoL: global health status; physical, cognitive, role, social, and emotional functioning; itchy skin;

pain; and weakness of legs. We hypothesized that any burden of carrying the device (on physical functioning and itchy skin) or detriment to social and role functioning due to the visibility of the therapy may be balanced by patients' feeling of well-being (global health status and emotional functioning) related to active participation of both the patient and the caregiver in the fight against cancer and increasing patient empowerment. Moreover, we hypothesized that treatment with TTFields would not have an influence on cognitive functioning, pain, and weakness of legs.

Statistical Analysis

Calculation of HRQoL Scores

The items on both questionnaires were scaled and scored using the recommended EORTC procedures.²¹ Raw scores were transformed to a linear scale ranging from 0 to 100, with a higher score representing a higher level of functioning or higher level of symptoms. The results of this study are presented in accordance with guidelines for reporting HRQoL in cancer clinical trials and methods.²²⁻²⁴ Differences of at least 10 points (on a 0-100 scale) were classified as the minimum clinically meaningful change in any HRQoL scale/item.²⁴

Descriptive Statistics

Descriptive statistics were used to report HRQoL scores as well as the sociodemographic and clinical variables for the population of patients who completed at least 1 HRQoL scale at baseline separately for both treatment groups. Means and SDs or medians and ranges were calculated for continuous variables depending on the distribution of the variable. Frequencies and percentages were calculated for nominal variables. Differences between arms were tested using a 2-sided χ^2 test or an independent 2-tailed, unpaired *t* test or Mann-Whitney test at an α value of .05 for each variable.

Adherence to HRQoL assessments was calculated as the number of forms received divided by the number of forms expected at every assessment. Patients who completed the assessments at the time of progression were included in this analysis.

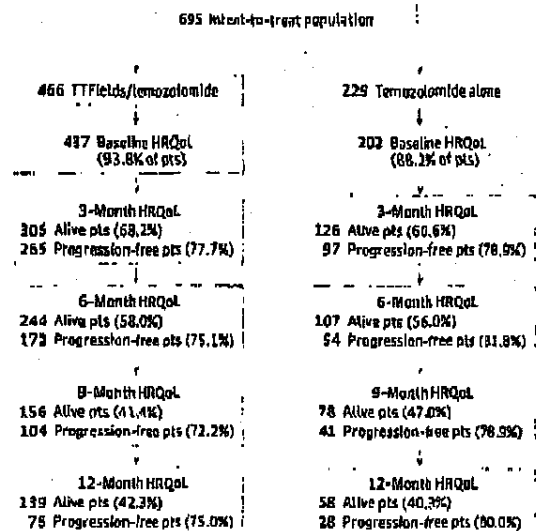
HRQoL Scores Over Time

Mean HRQoL scores over time were calculated as well as the mean changes from baseline. A stable HRQoL score was defined as a change of less than 10 points, and a change of 10 or more points indicated a deterioration or improvement depending on the scale or item. Mean change from baseline was plotted to evaluate the longitudinal course of patients' experience of disease and treatment, and a linear mixed-model repeated-measures analysis was used to estimate the treatment effect over time. A sensitivity analysis of complete cases using multiple imputations with a predictive mean matching regression model was used to check the robustness of the treatment effect over time. An additional sensitivity analysis used a repeated-measures model that assumes there is random variation among participants that is related to the time of dropout.

Stable or Improved HRQoL During the Progression-Free Period

The percentage of patients with stable (<10-point change) or improved (≥ 10 -point change) HRQoL during the progression-

Figure 1. Consort Diagram



Data are the number and percentage of patients in the categories (baseline, alive, and progression-free) who completed the health-related quality-of-life (HRQoL) questionnaire at the indicated times. pts indicates patients; TTFields, tumor-treating fields.

free period, thus excluding the HRQoL assessment at progression, was determined separately for both treatment arms. This calculation was based on the total number of patients with a valid baseline HRQoL assessment and at least 1 additional follow-up assessment. Moreover, the area under the curve of stable or improved HRQoL for the entire duration of stability or improvement was determined, and differences between arms were assessed with the trapezoidal method (eAppendix 2 in Supplement 1).

Deterioration-Free Survival and Time to Deterioration

Deterioration-free survival was defined as the time to a greater than 10-point deterioration in scores from baseline without a subsequent 10-point or more improvement in scores compared with baseline, progressive disease, or death in the absence of a previous definitive deterioration before the next assessment. Disease progression was included as a surrogate measure. Data were censored at the last HRQoL assessment date for patients with a change of less than 10 points, patients who did not progress, or patients who died after 9 weeks since the last assessment. Data for patients with missing baseline scores were not included, and patients missing all postbaseline HRQoL assessments were censored at randomization. Time to deterioration (TTD) was defined similarly to deterioration-free survival, with the exception that progressive disease was excluded as an event (ie, nonmissing HRQoL data beyond progression were included). Kaplan-Meier methodology was used to estimate deterioration-free survival and TTD distributions and median times, and 95% CIs were computed using the Greenwood formula. The difference between treatment arms

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Table 1. Baseline Demographic and Disease Characteristics

| Characteristic | TTFields Plus Temozolomide (n = 437) | Temozolomide (n = 202) | All Patients (N = 639) | P Value |
|-----------------------------------------------------------------|--------------------------------------------|---------------------------|---------------------------|---------|
| Age, y | | | | |
| Mean (SD) | 54.6 (11.4) | 55.2 (11.6) | 54.8 (11.5) | .50 |
| Median (range) | 56.0 (19-83) | 57.0 (19-80) | 56.0 (19-83) | |
| Sex, No. (%) | | | | |
| Male | 297 (68.0) | 140 (69.3) | 437 (68.4) | |
| Female | 140 (32.0) | 62 (30.7) | 202 (31.6) | .73 |
| Antiepileptic medication at baseline, No. (%) | 174 (39.8) | 79 (39.1) | 253 (39.6) | .87 |
| Corticosteroid therapy at baseline, No. (%) | 129 (29.5) | 60 (29.7) | 189 (29.6) | .96 |
| Region, No. (%) | | | | |
| United States | 203 (46.5) | 97 (48.0) | 300 (46.9) | |
| Canada, Europe, Israel, and Korea | 234 (53.5) | 105 (52.0) | 339 (53.1) | .71 |
| Extent of resection, No. (%) | | | | |
| Biopsy | 55 (12.6) | 24 (11.9) | 79 (12.4) | |
| Partial resection | 149 (34.1) | 70 (34.7) | 219 (34.3) | .97 |
| Gross total resection | 233 (53.3) | 108 (53.5) | 341 (53.4) | |
| Tumor position, No. (%) ^a | | | | |
| Corpus callosum | 23 (5.3) | 12 (5.9) | 35 (5.5) | |
| Frontal lobe | 177 (40.5) | 74 (36.6) | 251 (39.3) | |
| Occipital lobe | 55 (12.6) | 24 (11.9) | 79 (12.4) | |
| Parietal lobe | 138 (31.6) | 78 (38.6) | 216 (33.8) | .66 |
| Temporal lobe | 179 (41.0) | 81 (40.1) | 260 (40.7) | |
| Missing | 2 (<1) | 2 (1.0) | 4 (0.6) | |
| Tumor location, No. (%) ^a | | | | |
| Left | 202 (46.2) | 84 (41.6) | 286 (44.8) | |
| Right | 234 (53.5) | 116 (57.4) | 350 (54.8) | .65 |
| Both | 4 (0.9) | 2 (1.0) | 6 (0.9) | |
| Corpus callosum | 14 (3.2) | 9 (4.5) | 23 (3.6) | |
| Completed radiotherapy, No. (%) | | | | |
| <57 Gy | 20 (4.6) | 10 (5.0) | 30 (4.7) | |
| 60 Gy (standard; ±5%) | 399 (91.3) | 188 (93.1) | 587 (91.9) | .38 |
| >63 Gy | 15 (3.4) | 3 (1.5) | 18 (2.8) | |
| Missing | 3 (0.7) | 1 (0.5) | 4 (0.6) | |
| Karnofsky performance score | | | | |
| Median (range) | 90 (60-100) | 90 (70-100) | 90 (60-100) | .26 |
| Baseline Mini-Mental State Examination score available, No. (%) | | | | |
| ≤26 | 81 (18.9) | 43 (22.2) | 124 (19.9) | |
| 27-30 | 348 (81.2) | 151 (77.8) | 499 (80.1) | .34 |
| Cycles (months) of treatment with TTFields | | NA | NA | NA |
| No | 425 | | | |
| Mean (SD) | 12.5 (11.8) | | | |
| Median (range) | 8.3 (0-82) | | | |
| Cycles of treatment with temozolomide | | | | |
| No | 430 | 192 | 622 | |
| Mean (SD) | 8.9 (8.3) | 7.5 (6.2) | 8.5 (7.8) | .02 |
| Median (range) | 6.2 (0-51) | 5.5 (0-33) | 5.9 (0-51) | |
| Adherence to TTFields therapy ^b | 327 (74.8) | NA | NA | NA |

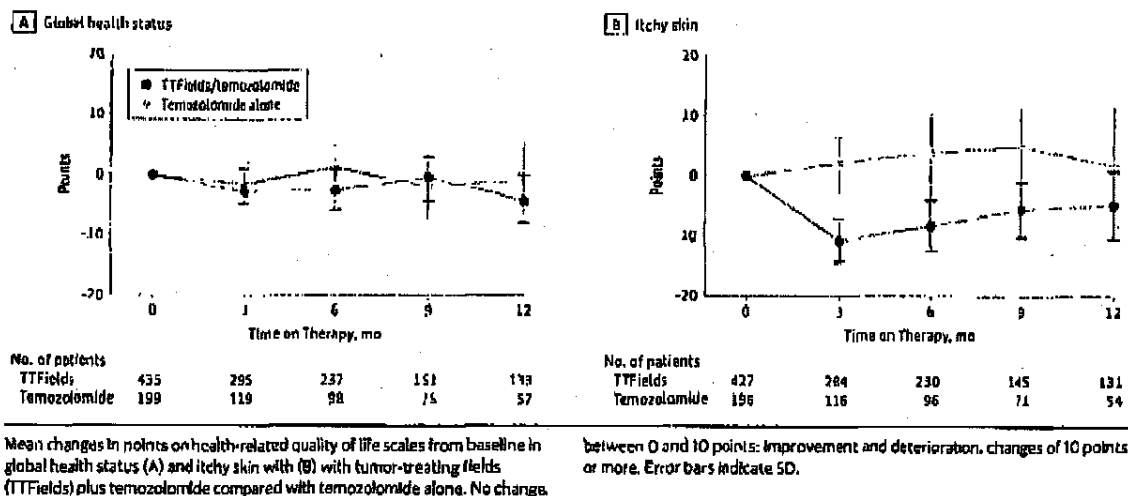
Abbreviations: Gy, gray; NA, not applicable; TTFields, tumor-treating fields.

^a Multiple locations possible.^b Defined as use of the device 75% or more of the time during the first 3 months of treatment.

was compared using a 2-sided stratified log-rank test. Hazard ratios were estimated using a stratified (for extent of resection and MGMT status) Cox proportional hazards regression model.

SAS, version 9.4 (SAS Institute) was used for all statistical analyses, and comparisons between groups were based on the intent-to-treat principle. P values <.05 were considered to be

Figure 2. Changes in Global Health Status and Itchy Skin



statistically significant. The Hochberg procedure was used to adjust for the multiplicity of treatment comparisons in the preselected HRQoL scales analyses.

Results

Patients

A total of 695 patients were randomly assigned in a 2:1 ratio to TTFields plus temozolomide ($n = 466$) or temozolomide alone ($n = 229$). A total of 639 (91.9%) patients completed at least 1 HRQoL scale at baseline: 437 (93.8%) of those in the TTFields plus temozolomide arm and 202 (88.2%) patients in temozolomide-alone arm (Figure 1). The baseline demographics of the patients who provided HRQoL data were comparable to those of the intention-to-treat population¹⁵ and were well balanced between treatment arms in this subpopulation (Table 1).

HRQoL Completion Rates and Baseline Scores

Adherence to HRQoL assessments decreased from 91.9% at baseline to 65.8% (431 of 655 patients alive) at 3 months and dropped to 41.7% (197 of 473 patients alive) at 12 months of follow-up (Figure 1). Mean and median baseline HRQoL scores were comparable between arms for all preselected scales/items (eTable 1 in Supplement 1), as well as the exploratory scales and items. Reference values of HRQoL scores of a healthy general population²⁵ were available for 7 of 9 predefined scales and items (except itchy skin and weakness of legs). Patients with glioblastoma after completion of radiochemotherapy showed clinically relevant worse functioning or more symptoms compared with the general population on all scales except pain, which was similar.²⁵

Mean Changes in HRQoL From Baseline and the Repeated-Measures Mixed-Effect Model

Mean changes in HRQoL over time for the global health status is presented in Figure 2A and for all 9 predefined HRQoL scales

in the eFigure in Supplement 1. Throughout the 12-month assessment period, mean changes from baseline were stable (<10-point change from baseline) for all 9 predefined HRQoL scales in both treatment arms (eFigure in Supplement 1) with the exception of itchy skin (Figure 2B). For itchy skin, a clinically relevant deterioration (ie, an increase in itchy skin) compared with baseline was seen at the month 3 evaluation in the TTFields plus temozolomide arm (mean [SD] increase, 10.4 [30.1] points vs an improvement of 2.3 [24.4] points in the temozolomide arm). For differences between treatment arms, patients treated with TTFields plus temozolomide had significantly and clinically relevant worse itchy skin at 3, 6, and 9 months than patients treated with temozolomide alone, but not at 12 months (mean [SD] increase of 10.4 [30.1] in the TTFields plus temozolomide arm vs a decrease of 2.3 [24.4] in the temozolomide-alone arm, $P = .005$; increase of 8.1 [31.6] in the TTFields plus temozolomide arm vs a decrease of 4.2 [31.4] in the temozolomide-alone arm, $P = .008$; increase of 5.3 [28.0] in the TTFields plus temozolomide arm vs a decrease of 5.2 [29.6] in the temozolomide-alone arm, $P = .04$; increase of 4.6 [32.8] in the TTFields plus temozolomide arm vs a decrease of 1.9 [36.9] in the temozolomide-alone arm, $P = .66$, respectively). For all other scales, there were no statistically significant or clinically relevant differences between treatment arms.

The repeated-measures mixed-effect model supported this finding, with no statistically significant difference between treatment arms in HRQoL scores over time in any predefined scale or item except for itchy skin ($P < .001$), which was worse in the TTFields plus temozolomide arm (eTable 2 in Supplement 1). The sensitivity analyses showed that the results of the linear mixed model were robust.

Stable or Improved HRQoL During Progression-Free Time
Compared with baseline, more patients in the TTFields plus temozolomide arm compared with the temozolomide-alone arm reported stable or improved scores for global health status (53.5% vs 38.0%, respectively, $P = .001$), physical func-

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Table 2. Stable or Improved Health-Related Quality of Life During Progression-Free Time

| Characteristic | TFields Plus Temozolomide (n = 361) | Temozolomide (n = 142) | P Value | α Value |
|--------------------------------------------------------------|-------------------------------------------|---------------------------|---------|---------|
| Pain | | | | |
| Stable/improved from baseline, No./No. (%) | 205/361 (56.8) | 51/142 (35.9) | <.001 | .05 |
| Median duration (95% CI), mo | 6.2 (5.9 to 7.0) | 6.3 (5.6 to 9.1) | .88 | |
| Median CFB AUC until last stable/improved status (95% CI) | 0 (0 to 0) | 0 (0 to 0) | .80 | |
| Global health status | | | | |
| Stable/improved from baseline, No./No. (%) | 192/359 (53.5) | 53/141 (37.6) | .001 | .025 |
| Median duration (95% CI), mo | 6.3 (5.9 to 7.4) | 7.9 (5.9 to 9.8) | .24 | |
| Median CFB AUC until last stable/improved status (95% CI) | 24.4 (11.9 to 35.0) | 55.9 (13.1 to 121.3) | .13 | |
| Physical functioning | | | | |
| Stable/improved from baseline, No./No. (%) | 195/361 (54.0) | 54/142 (38.0) | .001 | .017 |
| Median duration (95% CI), mo | 6.2 (5.9 to 8.2) | 9.1 (5.9 to 9.8) | .21 | |
| Median CFB AUC until last stable/improved status (95% CI) | 0 (0 to 18.7) | 0 (0 to 30.0) | .53 | |
| Weakness of legs | | | | |
| Stable/improved from baseline, No./No. (%) | 206/351 (58.7) | 58/138 (42.0) | .001 | .013 |
| Median duration (95% CI), mo | 6.3 (6.0 to 8.3) | 9.1 (5.9 to 9.8) | .08 | |
| Median CFB AUC until last stable/improved status (95% CI) | 0 (0 to 0) | 0 (0 to 0) | .51 | |
| Cognitive functioning | | | | |
| Stable/improved from baseline, No./No. (%) | 181/359 (50.4) | 55/142 (38.7) | .02 | .01 |
| Median duration (95% CI), mo | 6.0 (4.9 to 6.5) | 6.2 (5.7 to 9.6) | .65 | |
| Median CFB AUC until last stable/improved status (95% CI) | 28.3 (0 to 48.6) | 0 (0 to 23.3) | .37 | |
| Emotional functioning | | | | |
| Stable/improved from baseline, No./No. (%) | 196/359 (54.6) | 62/142 (43.7) | .03 | .008 |
| Median duration (95% CI), mo | 6.3 (6.0 to 8.3) | 7.7 (5.8 to 9.4) | .38 | |
| Median CFB AUC until last stable/improved status (95% CI) | 22.6 (5.8 to 35.0) | 25.2 (0 to 54.4) | .73 | |
| Social functioning | | | | |
| Stable/improved from baseline, No./No. (%) | 173/359 (48.2) | 58/142 (40.8) | .14 | .007 |
| Median duration (95% CI), mo | 6.2 (5.9 to 7.1) | 6.7 (5.9 to 9.6) | .40 | |
| Median CFB AUC until last stable/improved status (95% CI) | 16.5 (0 to 47.2) | 0 (0 to 54.4) | .90 | |
| Role functioning | | | | |
| Stable/improved from baseline, No./No. (%) | 172/361 (47.9) | 58/141 (41.1) | .17 | .006 |
| Median duration (95% CI), mo | 5.9 (4.4 to 6.3) | 7.3 (5.7 to 9.3) | .27 | |
| Median CFB AUC until last stable/improved status (95% CI) | 0 (0 to 25.0) | 46.7 (0 to 75.8) | .34 | |
| Itchy skin | | | | |
| Stable/improved from baseline, No./No. (%) | 148/349 (42.4) | 64/137 (46.7) | .39 | .0056 |
| Median duration (95% CI), mo | 6.0 (4.7 to 6.3) | 6.7 (5.6 to 9.4) | .37 | |
| Median CFB AUC until last stable/improved status (95% CI) | 0 (0 to 0) | 0 (-102.2 to 0) | .19 | |

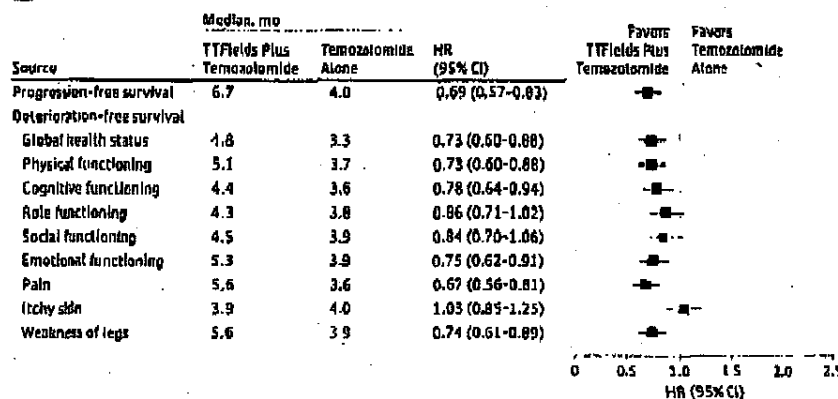
Abbreviations: AUC, area under the curve; CFB, change from baseline; TFields, tumor-treating fields.

tioning (54.0% vs 37.0%, respectively; $P = .001$), pain (56.8% vs 35.9%, respectively; $P < .001$), and weakness of legs (58.7% vs 42.0%, respectively; $P = .001$) but not in any of the other HRQoL scales and items. However, the duration of stable or improved HRQoL was shorter in the TFields plus temozolomide arm, although not significantly different from the temozolomide arm for any of the HRQoL scales and items. Overall, with a combination of these measures, the area under the curve analysis showed no significant differences between treatment arms for any of the HRQoL scales and items, indicating a similar HRQoL between treatment arms while patients did not experience tumor progression (Table 2).

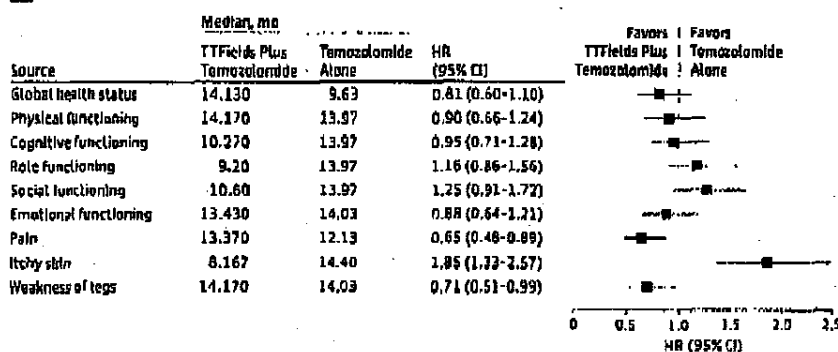
temozolomide arm for any of the HRQoL scales and items. Overall, with a combination of these measures, the area under the curve analysis showed no significant differences between treatment arms for any of the HRQoL scales and items, indicating a similar HRQoL between treatment arms while patients did not experience tumor progression (Table 2).

Figure 3. Deterioration-Free Survival and Time to Deterioration

A Deterioration-free survival



B Time to deterioration



Deterioration-free survival (A) and time to deterioration (B) for health-related quality-of-life domains in patients who received tumor-treating fields (TTFields) plus temozolomide compared with temozolomide alone. HR indicates hazard ratio.

Deterioration-Free Survival and TTD

The addition of TTFields to standard temozolomide chemotherapy resulted in statistically significant longer deterioration-free survival in global health status, physical and emotional functioning, pain, and weakness of legs (Figure 3A and eTable 2 in Supplement 1); the significant difference remained after correction for multiple testing. When progression was removed as a deterioration event (TTD), there was no negative influence of TTFields plus temozolomide treatment on the TTD of HRQoL (Figure 3B) except for itchy skin, which was worse in the TTFields plus temozolomide arm (8.2 vs 14.4 months). In contrast, the addition of TTFields to temozolomide resulted in a statistically significant prolongation until deterioration for pain (13.4 vs 12.1 months, $P < .01$). There were no other significant differences in TTD between arms (Figure 3B).

Discussion

In our detailed analysis of HRQoL during therapy with TTFields in addition to temozolomide, no significant difference was found between the groups in patients' HRQoL over time except for the skin reaction. As expected, itchy skin was reported more frequently in patients treated with TTFields be-

cause of the transducer arrays that have to be placed on the scalp of the patient. Consistently, over half of the patients also reported skin irritation as an adverse event. We had hypothesized that patients treated with TTFields may have better HRQoL in some domains as a result of active participation in the fight against cancer and the frequent interactions between patients and caregivers and device technicians regarding the device. However, on a group level, global health status and emotional functioning were not significantly different between treatment arms. Likewise, our hypotheses that the addition of TTFields would result in worse role and social functioning (due to the visibility of the device) and worse physical functioning were not confirmed. In line with our hypotheses, cognitive functioning, pain, and weakness of legs were not negatively affected by the addition of TTFields to temozolomide treatment. Most relevant for patients, HRQoL was maintained (in 8 of 9 of the predefined scales/items) over time. Combining the results of the survival and HRQoL analyses suggests that the addition of TTFields to adjuvant temozolomide is of value to patients with glioblastoma.

Patients who received TTFields had significantly longer deterioration-free survival compared with those in the temozolomide-alone arm for global health status (4.8 vs 3.3 months; $P < .01$), physical (5.1 vs 3.7 months; $P < .01$) and

emotional functioning (5.3 vs 3.9 months; $P < .01$), pain (5.6 vs 3.6 months; $P < .01$), and weakness of legs (5.6 vs 3.9 months; $P < .01$). For the other scales and items, there was no significant difference in deterioration-free survival between the 2 treatment arms. The prolonged deterioration-free survival for these scales is explained by the extended progression-free survival for patients in the combined TTFs plus temozolomide arm, as progressive disease is included as an event in this analysis. Therefore, TTD analyses, excluding progressive disease as an event, is important to illustrate the influence of a treatment on HRQoL. TTD was not significantly different across any HRQoL scale or item in TTFs-treated patients except for pain and itchy skin, indicating that treatment with TTFs had an influence only on the level of pain and itchy skin. In patients treated with TTFs, TTD was significantly longer for pain (13.4 vs 12.1 months; $P < .01$) and significantly shorter for itchy skin (8.2 vs 14.4 months; $P < .001$). The difference between deterioration-free survival and TTD indicates the importance of disease progression (rather than treatment) as a key event driving HRQoL decline, as suggested by previous studies.^{26,27} Moreover, in only 1% of patients, regardless of treatment arm, was a clinically relevant improvement in HRQoL seen after initial deterioration, supporting this observation. Taken together, the results of the deterioration-free survival and TTD analyses support the results of the longitudinal analysis by showing that the addition of TTFs to the standard of care did not adversely affect HRQoL. In fact, the delay in TTD for pain seen in TTFs-treated patients may reflect a delay in the occurrence of tumor-related headaches (although not significant, patients in the TTFs plus temozolomide arm had a longer TTD compared with patients in the temozolomide-alone arm for headaches: hazard ratio, 0.77; 95% CI, 0.54–1.10; $P = .16$). Future studies are needed to better understand this finding, as the median TTD values for pain were longer than the median progression-free survival for both arms.

Limitations

A common problem in many cancer clinical trials, as in this study, is missing HRQoL data. This absence is especially apparent during the follow-up period, hampering longitudinal data analysis. Patients with better prognostic factors and a good treatment response will be overrepresented at later stages.^{28,29} However, our mixed-model analyses, accounting for missing data, confirmed the results found in the mean change from baseline analyses. Another limitation of clinical trials is generalizability of results—patients in clinical trials may not be representative of a general glioblastoma population. Patients in this trial were included only if they successfully completed the combined radiochemotherapy. In addition, it may be that not all patients are prepared to accept wearing the TTFs device. Nevertheless, patients participating in this trial were similar with respect to clinical characteristics to those participating in the EORTC 26981 study¹² comparing radiotherapy alone with radiotherapy plus temozolomide. Lastly, many factors may affect HRQoL, such as age, comorbidity, tumor characteristics, previous antitumor treatment (eg, radiation dose), and supportive treatment. However, it is unlikely that these factors influenced our conclusion, as the objective of this study was to compare HRQoL results between 2 treatment arms in which patients were similar due to randomization.

Conclusions

Use of TTFs prolongs progression-free and overall survival in patients with glioblastoma. The addition of this novel device-delivered treatment neither negatively affects nor improves functioning and well-being of the patient, including critical HRQoL issues, such as role, social, and physical functioning. Patients reported more itchy skin, which is a direct and expected consequence of the placement of transducer arrays on the patients' scalp. Considering the net clinical benefit, our HRQoL data support the addition of TTFs to standard therapy in patients with glioblastoma.

ARTICLE INFORMATION

Accepted for Publication: November 12, 2017.

Published Online: February 1, 2018.
doi:10.1001/jamaoncol.2017.5082

Open Access: This article is published under the JAMA license and is free to read on the day of publication.

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Author Contributions: Drs Taphoorn and Dirven contributed equally to the study. Drs Stupp and Kirson had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data: All authors.

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Study supervision: Bruna, Roth, Desai, Villano, Kirson, Ram, Stupp.

Conflict of Interest Disclosures: Dr Taphoorn has performed paid consultancy for Hoffmann-La Roche. Dr Lavy-Shahaf is an employee of and received personal fees from Novocure during the conduct of the study. Drs Weinberg and Kirson are employees of and own minority stock in Novocure. Dr Tallibert received fees from Centre-de-Recherche-en-Neuro-Oncologie for enrolling patients at Salpêtrière University Hospital during the conduct of the study. Dr Dabbal received research support from Foundation ARC, IntselChimos, Beta-Ionov, and Carthera and travel support from Carthera and Hoffmann-La Roche and served as a paid member of the advisory boards of BMS, Hoffmann-La Roche, and Lettra du Cancérologue. Dr Hottinger received research support from Novocure and served on advisory boards of Servier and BMS (fees paid to the institution). Dr Roth served as a paid member of the advisory boards of Roche and MSD and received personal fees for lectures on behalf of BMS and Novocure. Dr Ram received grants and personal fees from and owns minority stock in Novocure. Dr Stupp received nonfinancial support from Novocure, and his institution received fees from Celgene, Novartis, AbbVie, Merck KGaA (Darmstadt), and MSD-Merck & Co. Dr Stupp's spouse is a full-time employee of Celgene. No other conflicts were reported.

Funding/Support: The study was funded by Novocure Ltd.

Role of the Funder/Sponsor: Novocure Ltd had a role in the design and conduct of the study; collection, management, and analysis of the data; and decision to submit the manuscript for publication. The study was designed by Drs Stupp and Ram, together with representatives from Novocure, mainly Dr Kirson. The study oversight was supported and monitored by a clinical research organization, which also held the database. Data were collected by the investigators and monitored by the clinical research organization. The statistical analysis plan for the quality of life analyses was developed by Drs Taphoorn, Dirven, Kirson, and Lavy-Shahaf, the sponsor's statistician. Data interpretation was the responsibility of Drs Taphoorn, Dirven, Kirson, and Stupp. The first draft of this manuscript was developed by Drs Taphoorn, Dirven, Kirson, and Stupp. A subsequent mature draft and prefinal version were circulated among all authors who gave additional input, contributed to, and approved the manuscript. The decision to publish the data and its interpretation was made by Drs Stupp and Ram and was supported by all coauthors.

Meeting Presentations: This research was presented as a late-breaking oral presentation at the 2017 American Society for Radiation Oncology Annual Meeting, September 24, 2017; San Diego, California.

Additional Contributions: We thank the patients and their families for participating in the trial. We

are grateful to all study investigators, nurses, and supporting staff for providing care to the patients and data management.

Additional Information: The study oversight was supported and monitored by a clinical research organization that also held the database. The clinical research organization varied among countries and each was paid by Novocure Ltd.

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JAMA | Original Investigation

Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma

A Randomized Clinical Trial

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IMPORTANCE Tumor-treating fields (TTFields) is an antimitotic treatment modality that interferes with glioblastoma cell division and organelle assembly by delivering low-intensity alternating electric fields to the tumor.

OBJECTIVE To investigate whether TTFields improves progression-free and overall survival of patients with glioblastoma, a fatal disease that commonly recurs at the initial tumor site or in the central nervous system.

DESIGN, SETTING, AND PARTICIPANTS In this randomized, open-label trial, 695 patients with glioblastoma whose tumor was resected or biopsied and had completed concomitant radiochemotherapy (median time from diagnosis to randomization, 3.8 months) were enrolled at 83 centers (July 2009-2014) and followed up through December 2016. A preliminary report from this trial was published in 2015; this report describes the final analysis.

INTERVENTIONS Patients were randomized 2:1 to TTFields plus maintenance temozolomide chemotherapy (n = 466) or temozolomide alone (n = 229). The TTFields, consisting of low-intensity, 200 kHz frequency, alternating electric fields, was delivered (≈ 18 hours/d) via 4 transducer arrays on the shaved scalp and connected to a portable device. Temozolomide was administered to both groups (150-200 mg/m²) for 5 days per 28-day cycle (6-12 cycles).




MAIN OUTCOMES AND MEASURES Progression-free survival (tested at $\alpha = .046$). The secondary end point was overall survival (tested hierarchically at $\alpha = .048$). Analyses were performed for the intent-to-treat population. Adverse events were compared by group.

RESULTS Of the 695 randomized patients (median age, 56 years; IQR, 48-63; 473 men [68%]), 637 (92%) completed the trial. Median progression-free survival from randomization was 6.7 months in the TTFields-temozolomide group and 4.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.52-0.76; $P < .001$). Median overall survival was 20.9 months in the TTFields-temozolomide group vs 16.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76; $P < .001$). Systemic adverse event frequency was 48% in the TTFields-temozolomide group and 44% in the temozolomide-alone group. Mild to moderate skin toxicity underneath the transducer arrays occurred in 52% of patients who received TTFields-temozolomide vs no patients who received temozolomide alone.

CONCLUSIONS AND RELEVANCE In the final analysis of this randomized clinical trial of patients with glioblastoma who had received standard radiochemotherapy, the addition of TTFields to maintenance temozolomide chemotherapy vs maintenance temozolomide alone, resulted in statistically significant improvement in progression-free survival and overall survival. These results are consistent with the previous interim analysis.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00916409

JAMA. 2017;318(23):2306-2316. doi:10.1001/jama.2017.8718

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Glioblastoma is the most common and aggressive primary brain tumor with an annual incidence of 3.19 per 100 000.^{1,2} The disease course is typically rapid, with only approximately 1 in 4 patients alive 2 years after diagnosis, and only 5% to 10% of patients alive at 5 years.^{1,3,7}

Since the current standard of care was established, consisting of surgical resection or biopsy, followed by radiotherapy with concomitant temozolomide chemotherapy, followed by maintenance temozolomide for 6 to 12 months,⁸ little progress has been made in the treatment of this disease.^{1,3,9} Most trials have shown median progression-free survival and median overall survival from diagnosis of 6.2 to 7.5 months and 14.6 to 16.7 months, respectively.^{4-6,8}

Tumor-treating fields (TTFields) are an antimitotic treatment that selectively affects dividing glioblastoma cells by delivering low-intensity, intermediate-frequency (200 kHz) alternating electric fields via transducer arrays applied to the scalp.^{10,11} Tumor-treating fields cause mitotic arrest and apoptosis of rapidly dividing cells.^{10,11} Preclinical studies demonstrated increased sensitivity to chemotherapy with the addition of TTFields in human glioblastoma cell lines and in animal tumor models.¹² In a randomized phase 3 trial involving 237 patients with recurrent glioblastoma whose several lines of prior therapy had failed, TTFields monotherapy was compared with the treating physicians' best choice of salvage chemotherapy. Although no survival difference was observed, the higher objective response rate (12% vs 7%) suggested single-modality activity of TTFields.¹³

In 2009, this randomized phase 3 clinical trial was initiated, comparing maintenance temozolomide alone with maintenance temozolomide in combination with TTFields among patients with glioblastoma. A preplanned interim analysis involving the first 315 patients randomized was previously reported and demonstrated improved progression-free and overall survival.¹⁴ This article reports the final analysis involving all 695 randomized patients, with a median follow-up of 40 months and a minimum follow-up of 24 months.

Methods

The study was approved by the institutional review boards or ethics committees of all participating centers, and all patients provided written informed consent before entering the study. The trial protocol and statistical analysis plan are included in Supplement 1.

Study Population

Patients eligible for this study were aged 18 years or older, had a Karnofsky performance score of 70 or higher (a score of ≥70 ensures independence in activities of daily living), and had newly diagnosed and histologically confirmed supratentorial glioblastoma (World Health Organization [WHO] grade IV astrocytoma¹⁵). All participants had undergone maximal safe debulking surgery when feasible or biopsy and had completed standard radiotherapy with concomitant temozolomide at the time of enrollment. Prior use of implanted

Key Points

Question Does the use of tumor-treating fields (TTFields), consisting of low-intensity, alternating electric fields delivered via transducer arrays applied to the scalp, when added to maintenance temozolomide chemotherapy, improve progression-free survival for patients with glioblastoma?

Findings In this randomized clinical trial involving 695 patients with glioblastoma who had completed initial radiochemotherapy, median progression-free survival from randomization was 6.7 months in the TTFields plus temozolomide group and 4.0 months in the temozolomide-alone group (hazard ratio, 0.63), a significant difference.

Meaning Among patients with glioblastoma, the addition of TTFields to maintenance temozolomide chemotherapy resulted in statistically significant improvement in survival. These results are consistent with those reported in a previous interim analysis.

carbamustine wafers was allowed. Patients with evidence of progressive disease following radiochemotherapy, infratentorial tumor location, and severe comorbidities were excluded. Adequate hematological, liver, and kidney function tests to allow for temozolomide chemotherapy were required.^{8,14,16}

Study Design and Treatment

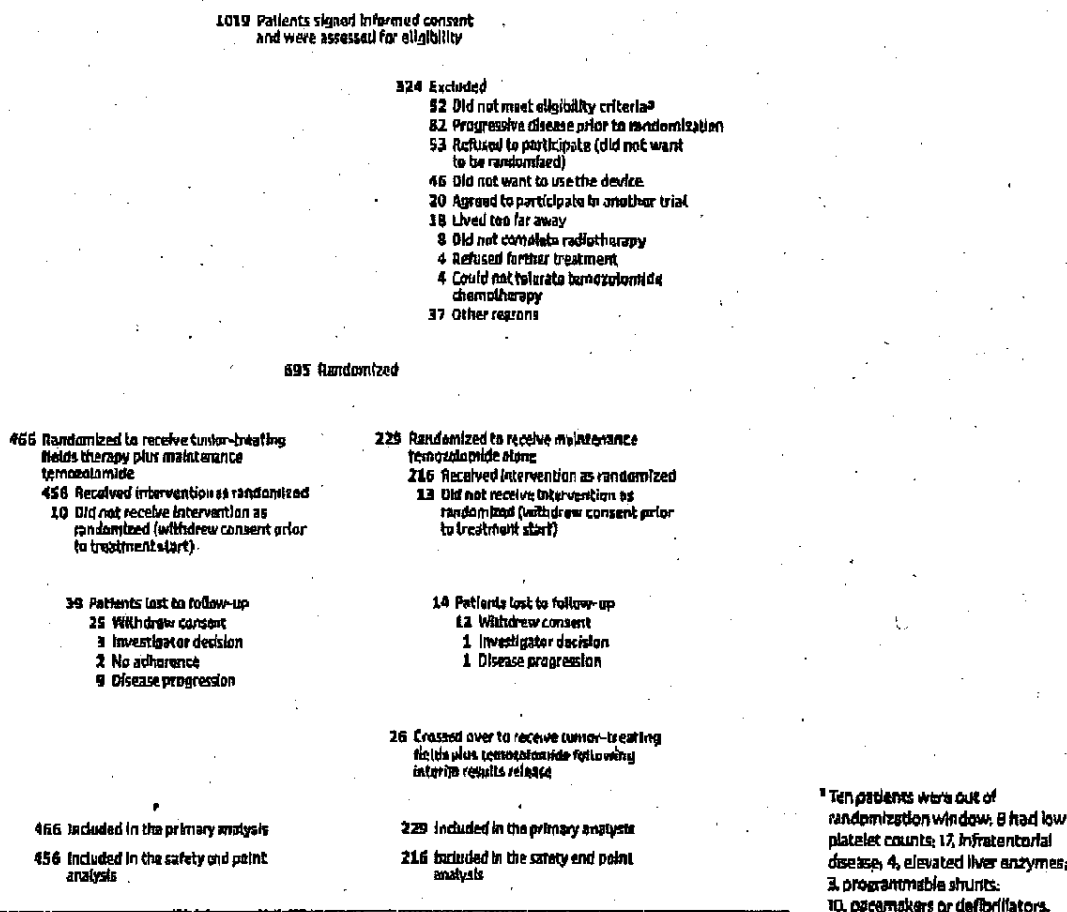
This multicenter, open-label, randomized clinical phase 3 trial, recruited 695 patients at 83 sites in North America, Europe, the Republic of Korea, and Israel. The trial was designed to test the efficacy and safety of TTFields in combination with best standard of care in the treatment of newly diagnosed glioblastoma. Patients were randomized after the end of radiochemotherapy at a ratio of 2:1 to receive standard maintenance temozolomide chemotherapy (150–200 mg/m²/d for 5 days every 28 days for 6 cycles) with or without the addition of TTFields. Tumor treating fields treatment was to be initiated at least 4 weeks but not more than 7 weeks from the last day of radiotherapy. Maintenance temozolomide was delivered in 28-day cycles according to the protocol established by the European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada (NCIC) Clinical Trials Group.⁸ Extension of the duration of maintenance temozolomide beyond 6 cycles was allowed per local practice. Randomization was performed using a central web-based randomization system and was stratified by extent of resection (biopsy, partial resection, gross total resection) and by the methylation status of the O6-methylguanine-DNA methyltransferase (MGMT) gene promoter (methylated, unmethylated, unknown).

Treatment with TTFields was delivered through 4 transducer arrays with 9 insulated electrodes each placed on the shaved scalp and connected to a portable device set to generate 200-kHz electric fields within the brain (Optune, Novocure Inc). Transducer array layouts were determined using a TTFields mapping software system to optimize field intensity within the treated tumor (NovoTAL, Novocure Inc). Patients were trained by the nursing staff and device technician to operate the device independently, replace transducer arrays, and troubleshoot any

Research Original Investigation

TTFields Plus Temozolomide vs Temozolomide on Glioblastoma

Figure 1. Recruitment and Inclusion of Patients in the Study



alarm conditions (eg, disconnected cables). All treatment was delivered on an outpatient basis and at home. The transducer arrays were supplied in individual sterile packages, and replaced by the patient, a caregiver, or a device technician twice a week. Although uninterrupted treatment was recommended, the patient could take short treatment breaks to tend to personal needs. The patient was advised to continue treatment for no fewer than 18 hours a day.

If tumor progression occurred, second-line therapy was offered per local practice. However, in the experimental group, TTFields could be continued until second radiologic progression occurred or for a maximum of 24 months.

Patient Surveillance and Follow-up

Patients diagnosed with glioblastoma who had undergone surgical resection or biopsy and had received standard radiochemotherapy were randomized to receive either TTFields plus temozolomide or temozolomide alone between July 2009 and December 2014 (Figure 1). The database was locked for final analysis on December 28, 2016. Baseline contrast-enhanced magnetic resonance imaging (MRI) of the brain was required within 2 weeks before starting treatment with maintenance

temozolomide with or without TTFields. A complete physical examination and laboratory parameters were performed within 1 week of treatment start. Evaluation also included the EORTC QLQ-C30 quality-of-life questionnaire with its brain-specific module (BN-20)^{27,28} and a Mini-Mental State Examination (a test result of 27-30 points is considered normal function). Patients were seen monthly for medical follow-up and routine laboratory examinations. Quality of life was assessed every 3 months.

Adverse events were recorded for 2 months after treatment discontinuation according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) v3.0. Adverse events were presented descriptively as number and percentage of patients with each adverse event term for all patients available at the time of the analysis.

Independent Radiological Review

Magnetic resonance imaging was performed at 2-month intervals until second progression. In the event of clinical progression, MRI was to be performed within 1 week after the investigator had become aware of it. All MRIs were reviewed by 2 blinded central independent radiologists (BioClinica Inc) and were evaluated for tumor response and progression (Macdonald criteria²⁹). For cases

In which the 2 reviewers were not in agreement, a third blinded radiologist adjudicated between them.

Central MGMT Testing, Pathology Review, and Molecular Analyses

In patients with paraffin-embedded tumor tissue available, evaluation of the MGMT methylation status was performed using quantitative methylation-specific polymerase chain reaction^{3,20} by a central laboratory licensed by MDxHealth. If the MGMT methylation status could not be determined centrally prior to randomization, local MGMT methylation status was used for stratification. All data analyses were based on the central blinded assessment.

Patients were included based on initial local histological diagnosis. A retrospective pathology review and evaluation of molecular testing was performed by a neuropathologist (B.L.) and molecular biologist (M.E.H.). Deletion of chromosomal arms 1p and 19q and amplification of the epidermal growth factor receptor (EGFR) were evaluated by fluorescent *in situ* hybridization (FISH), immunohistochemistry (IHC), or both; and the mutation status of the isocitrate dehydrogenase 1 (IDH1) gene was determined by immunohistochemistry for the most common mutant IDH1-R132H as described previously.²¹ For cases in which insufficient tissue was available for EGFR FISH, the result of EGFR IHC was used as a surrogate (Hirsch score, ≥ 200 amplified; <200 , not amplified).²²

Outcomes

Primary and Secondary End Points

The primary end point was progression-free survival, and the secondary end point was overall survival, with analyses conducted in the intent-to-treat population.

The protocol defined that overall survival would be analyzed in a per-protocol population including only patients who received their original allocated treatments. However, 26 patients (11%) in the temozolomide-alone control group crossed over and received TTFields after December 2014, following release of the results of the interim analysis of the trial. These 26 patients had more favorable baseline characteristics than the rest of the control patients (MGMT methylated, 48%; Karnofsky performance score, 80-100; time from end of radiotherapy to randomization, 31 days) and received more cycles of temozolomide (median, 10.5 cycles). To avoid possible bias, these patients were analyzed as randomized in the control group according to the intent-to-treat principle.

Exploratory End Points

Other predefined exploratory end points were percentage of patients alive and progression free at 6 months, annualized survival rates, quality of life, Mini-Mental State Examination, and Karnofsky performance score. The quality-of-life data are not reported in this article.

Statistical Analysis

Primary and Secondary End Points

For the primary end point of progression-free survival, the calculated sample size was 700 patients aimed to detect a hazard ratio (HR) of 0.78 or less, with 80% power allowing for 10%

loss to follow-up and a 2-sided $\alpha = .05$. Overall survival was a powered secondary end point in the study (80% power; HR, 0.76; 2-sided $\alpha = .05$). To avoid multiplicity, overall survival was to be tested statistically only if the primary end point of the study was met.

To allow for 2 analyses in the trial, the final type I error of 0.05 was split between the interim and final analyses based on a standard spending function (Lan and DeMets^{23,24}). The primary end point at the final analysis would be achieved if progression-free survival was significantly longer in the TTFields plus temozolomide group using a stratified log-rank test (stratified by the randomization strata) with an α of .046 (an α of 0.014 was spent on the interim analysis).

The secondary end point would be achieved at the final analysis if overall survival was significantly longer in the TTFields plus temozolomide group using a stratified log-rank test with an α of .048 (an α of .006 was spent on the interim analysis).

Missing Data

For the analysis of progression-free survival patients were censored for progression when treatment was changed before evidence of progression (at the date of treatment change), at the date of their last MRI if lost to follow up, or upon reaching the cutoff date without progression. For the analysis of overall survival, patients without a known date of death were censored at the last known date they were documented to be alive.

Exploratory End Points

The exploratory end points of annual survival rates and the rate of progression-free survival at 6 months were compared between groups using a 1-sided Z distribution of the Kaplan-Meier estimates of the survival rates at the defined time point. In addition, the Cox proportional hazards model was used to analyze both progression-free survival and overall survival controlling for treatment group, age, sex, MGMT methylation status (as determined by the central laboratory), tumor location in the brain, and country of residence (United States vs all other countries). The threshold for significant interactions in the model was specified at an α of .05.

Post Hoc Analysis

Post hoc analyses of prespecified subgroups (MGMT promoter methylation status, extent of resection (complete, partial resection, or biopsy), age (continuous), performance status (90-100 vs ≤ 80), sex, and geographic region (United States vs the rest of the world) was performed using a multivariate analysis testing the difference between treatment groups while controlling for the other prognostic factors.

Analysis of Adverse Events and Tolerability

Differences in the incidence of adverse events between groups was tested using a χ^2 test at an α of .05. The incidence of adverse events was also compared between groups after normalizing the incidence to the average treatment duration per group. Differences in the time to decline in Karnofsky performance score and Mini-Mental State Examination were tested using a log-rank test at an α of .05. All analyses were performed using SAS version 9.4.

Table 1. Patient and Treatment Characteristics

| Characteristics | No. (%) of Patients TTFields + Temozolomide (n = 456) | No. (%) of Patients Temozolomide Alone (n = 229) |
|--------------------------------------------------|----------------------------------------------------------------|-----------------------------------------------------------|
| Age, y | | |
| Median (range) | 56.0 (19-83) | 57.0 (19-80) |
| ≥65 | 89 (19) | 45 (20) |
| <65 | 377 (81) | 184 (80) |
| Karnofsky performance score ^a | | |
| Median (range) | 90.0 (60-100) | 90.0 (70-100) |
| 90-100 | 308 (66) | 149 (65) |
| ≤80 | 154 (33) | 74 (32) |
| Missing | 4 (1) | 6 (3) |
| Sex | | |
| Men | 316 (68) | 157 (69) |
| Women | 150 (32) | 72 (31) |
| Region | | |
| United States | 221 (47) | 118 (52) |
| Outside the United States | 245 (53) | 111 (48) |
| Race/ethnicity | | |
| White | 416 (89) | 201 (86) |
| African American | 3 (1) | 1 (<1) |
| Asian | 27 (6) | 19 (8) |
| Hispanic | 18 (4) | 7 (3) |
| American Indian | 1 (<1) | 1 (<1) |
| Antiepileptic drug use at baseline | 205 (44) | 95 (41) |
| Corticosteroid use at baseline | 135 (29) | 54 (24) |
| Mini-Mental State Examination score ^b | | |
| 27-30 | 356 (76) | 160 (70) |
| ≤26 | 88 (19) | 40 (17) |
| Missing | 22 (5) | 21 (9) |
| Extent of resection ^c | | |
| Biopsy | 60 (13) | 29 (12) |
| Partial resection | 157 (34) | 77 (33) |
| Gross total resection | 249 (53) | 123 (54) |
| MGMT promoter region methylation status | | |
| Tissue available and tested | 386 (83) | 185 (81) |
| Methylated | 137 (36) | 77 (42) |
| Unmethylated | 209 (54) | 95 (51) |
| Invalid | 40 (10) | 13 (7) |
| Slides available for central pathology review | 296 (64) | 138 (60) |
| Confirmed glioblastoma | 285 (96) | 134 (97) |
| WHO grade II or III glioma | 4 (1) | 2 (1) |
| Insufficient quality for diagnosis | 7 (2) | 2 (1) |
| IDH1-R132H status | | |
| Tissue available and tested | 260 (56) | 119 (52) |
| Mutated | 19 (7) | 6 (5) |
| Negative test results | 240 (92) | 113 (95) |
| Invalid | 1 (<1) | |
| EGFR status | | |
| Tissue available and tested | 252 (54) | 112 (49) |
| Amplified | 102 (41) | 43 (38) |
| Not amplified | 147 (58) | 69 (61) |
| Invalid | 3 (1) | 1 (1) |
| Tumor tissue chromosomes 1p and 19q | | |
| Tissue available and tested | 259 (56) | 112 (49) |
| Codeletion | 2 (1) | |
| Loss 1p only | 4 (2) | 1 (1) |
| Loss 19q only | 3 (1) | 3 (3) |
| Retained | 219 (92) | 102 (91) |
| Invalid | 11 (4) | 6 (5) |

(continued)

Table 1. Patient and Treatment Characteristics (continued)

| Characteristics | No. (%) of Patients TTFields + Temozolomide (n = 456) | No. (%) of Patients Temozolomide Alone (n = 229) |
|-------------------------------------------------------------------------------|----------------------------------------------------------------|-----------------------------------------------------------|
| Tumor position ^c | | |
| Corpus callosum | 25 (5) | 12 (5) |
| Frontal lobe | 190 (41) | 84 (37) |
| Occipital lobe | 58 (12) | 27 (12) |
| Parietal lobe | 146 (31) | 89 (39) |
| Temporal lobe | 191 (41) | 90 (40) |
| Missing | 3 (1) | 3 (1) |
| Tumor location ^c | | |
| Left hemisphere | 214 (46) | 99 (43) |
| Right hemisphere | 249 (53) | 127 (55) |
| Both hemispheres | 4 (1) | 2 (1) |
| Corpus callosum | 15 (3) | 9 (4) |
| Missing | 1 (<1) | 1 (<1) |
| Treatment delivery | | |
| Completed standard radiation therapy | | |
| 57-63 Gy | 422 (91) | 212 (93) |
| <57 Gy | 21 (5) | 11 (5) |
| >63 Gy | 18 (4) | 3 (1) |
| Dose not reported | 5 (1) | 3 (1) |
| Concomitant radiation therapy and temozolomide | | |
| Yes | 413 (93) | 212 (93) |
| No record available | 33 (7) | 17 (7) |
| Time from last day of radiation treatment to randomization, median (range), d | 37 (15-128) | 36 (15-70) |
| Time from initial diagnosis to randomization, median (range), mo | 3.8 (1.7-6.2) | 3.7 (1.4-6.3) |
| Temozolomide cycles, median (range) | 6 (0-51) | 5 (0-33) |
| Tumor-treating fields therapy | | |
| Duration, median (range), mo | 8.2 (0-82) | |
| ≥18 h/d (first 3 mo of treatment), mean | 347 (75) | |

Abbreviations: EGFR, epidermal growth factor receptor gene;

IDH1-R132H, isocitrate dehydrogenase 1 (IDH1) R132H mutation site;

MGMT, O⁶-methylguanine-DNA-methyltransferase gene;

TTFields, tumor-treating fields; WHO, World Health Organization.

^a Karnofsky performance score ranges from 0 to 100 in 10-point increments, with a higher score representing better performance status.^b Scores range from 1 to 30, with a higher score representing better cognitive function.^c Multiple positions for each patient allowed (for multifocal tumors).

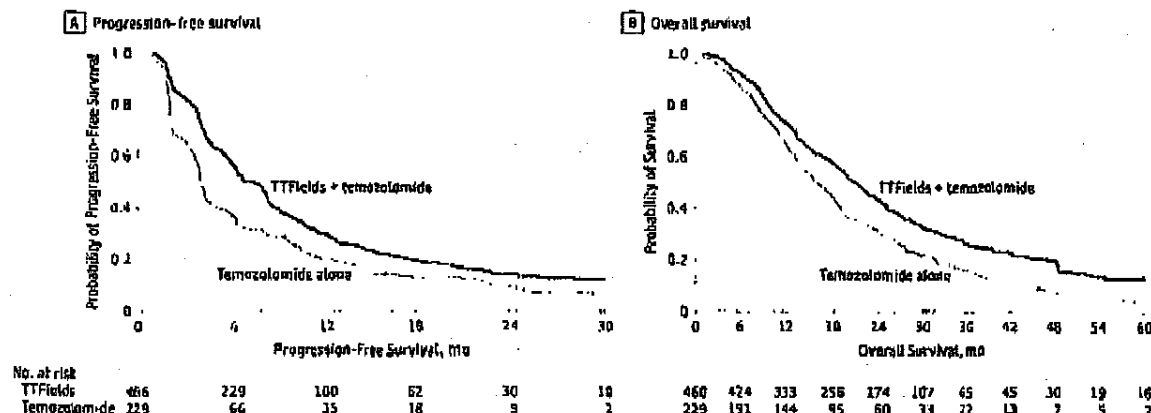
Results

Study Participants

Four hundred and sixty-six patients were randomized to receive TTFields plus temozolomide and 229 to receive temozolomide alone (Figure 1). Patient baseline characteristics were balanced between the 2 groups (Table 1). The median age was 56 years (interquartile range [IQR], 48-63 years), 68% were men, and median Karnofsky performance score was 90%. Eighty-nine percent of patients were white, and 49% of the patients were treated in the United States.

Fifty-four percent had undergone a gross total resection (>95% of the tumor removed; as assessed and reported by the surgeon), 13% of patients had a diagnostic biopsy only. Histological slides for central pathology review were available for

Figure 2. Kaplan-Meier Survival Curves for Patients Included in the Final Analysis in the Intent-to-Treat Population



A, Median progression-free survival from randomization for the tumor-treating fields (TTFields) plus temozolomide group was 6.7 months and was 4.0 months for the temozolomide-alone group (hazard ratio [HR], 0.63; 95% CI, 0.52-0.76; $P < .001$). B, Median survival from randomization was 20.9 months for the TTFields plus temozolomide group vs 16.0 months for the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76; $P < .001$). Median follow-up was 44 months (range, 25-91 months) in both groups.

434 of 695 patients (62%). The local diagnosis of glioblastoma was confirmed in 419 of 434 patients (97%). For 6 cases WHO grade II or III diagnoses were made, and for the remaining 9 patients, the available tissue for review did not allow for a definitive diagnosis or showed no tumor, yet all these patients were included in the intent-to-treat analysis. Tumor tissue for MGMT testing was available for 82% of the patients; of the cases with a valid test (518 of 571) 41% were MGMT methylated (40% TTFields plus temozolomide group and 45% for the temozolomide-only group). In 7% of tumors, expression of the IDH1-R132H mutant was demonstrated by a positive immunohistochemistry, EGFR was amplified in 40%.

Tumor location (lobe, hemisphere) in the brain was also comparable between the groups. The median time from histological diagnosis to randomization was 3.8 months (range, 1.7-6.2 months) for patients in the TTFields plus temozolomide group, and 3.7 months (range, 1.4-6.3 months) for those in the temozolomide-only group. Median time from the end of radiotherapy to randomization was 37 days in the TTFields plus temozolomide group and 36 days in the temozolomide-only group and occurred in most patients after starting of the first cycle of maintenance temozolomide. Median time from randomization to TTFields was 5 days (IQR, 3-7 days).

Treatment Delivery

All patients had completed radiotherapy and concomitant temozolomide as per local practice. The median number of temozolomide cycles until first tumor progression was 5 (range, 0-51) for the TTFields plus temozolomide group and 5 (range, 0-33) for the temozolomide-only group; the median duration of TTFields treatment was 8.2 months (range, 0-82 months), 51% ($n = 237$) of patients continued TTFields after the first progression.

Efficacy End points

After a median follow-up of 40 months (IQR, 34-66 months), and a minimum follow-up of 24 months, the primary end point

of median progression-free survival was 6.7 months (95% CI, 6.1-8.1 months) for patients treated with TTFields plus temozolomide vs 4.0 months (95% CI, 3.8-4.4 months) for patients treated with temozolomide alone, for a proportional hazard ratio (HR) of 0.63 (95% CI, 0.52-0.76; $P < .001$; stratified log-rank test; Figure 2A). For the secondary end point of overall survival, the median survival duration from randomization was 20.9 months (95% CI, 19.3-22.7 months) in the TTFields plus temozolomide group vs 16.0 months (95% CI, 14.0-18.4 months) in the temozolomide-only group, proportional HR of 0.63 (95% CI, 0.53-0.76; $P < .001$; stratified log-rank test; Figure 2B).

In exploratory analyses, the percentage of patients alive at 2 years from randomization was 43% (95% CI, 39%-48%); at 3 years, 26% (95% CI, 22%-31%), and at 5 years, 13% (95% CI, 9%-18%) in the TTFields plus temozolomide group and for the temozolomide-only group at 2 years was 31% (95% CI, 25%-38%; $P < .001$); at 3 years, 16% (95% CI, 12%-23%; $P = .009$); and at 5 years, 5% (95% CI, 2%-11%; $P = .004$). Progression-free survival at 6 months was 56% (95% CI, 51%-61%) for patients treated with TTFields plus temozolomide and 37% (95% CI, 30%-44%) with temozolomide only ($P < .001$) (Table 2).

An exploratory Cox proportional hazards model adjusting for Karnofsky performance score, MGMT promoter methylation status, geographic region, age, tumor location, and extent of resection were consistent with the findings of the progression-free and overall survival analyses. The following factors were associated with longer overall survival: TTFields plus temozolomide treatment (HR, 0.63; 95% CI, 0.53-0.76; $P < .001$), female sex (HR, 0.76; 95% CI, 0.63-0.92; $P = .005$), methylated MGMT promoter (HR, 0.50; 95% CI, 0.41-0.62; $P < .001$), younger age (as a continuous variable; HR, 0.978 per year; 95% CI, 0.969-0.985; $P < .001$) and higher Karnofsky performance score (as a categorical variable in 10 point increments; $P < .001$). Patients with frontal tumors had nonsignificantly longer survival (HR = 0.82, CI 0.67-1.01, $P = .061$). Country of treatment and extent of resection were not

Research Original Investigation

TTFields Plus Temozolomide vs Temozolomide on Glioblastoma

Table 2. Summary of Study End Points*

| | TTFields + Temozolomide (n = 466) | Temozolomide Alone (n = 229) | Between-Group Differences |
|-------------------------------------------|-----------------------------------------|------------------------------------|------------------------------|
| Progression-free survival | | | |
| Primary end point, median (95% CI), mo | 6.7 (5.1-8.1) | 4.0 (3.8-4.4) | 2.7 (2.1-4.2) |
| Overall survival | | | |
| Secondary end point, median (95% CI), mo | 20.9 (19.3-22.7) | 16.0 (14.0-18.4) | 4.9 (2.3-7.9) |
| Exploratory end points, % (95% CI) | | | |
| Progression-free 6-mo survival rate | 56 (51-61) | 37 (30-44) | 19 (15-23) |
| Annual survival rates, % | | | |
| 1 | 73 (69-77) | 65 (59-72) | 18 (10-25) |
| 2 | 43 (39-48) | 31 (25-38) | 12 (4-18) |
| 3 | 26 (22-31) | 16 (12-22) | 10 (3-17) |
| 4 | 20 (16-25) | 8 (4-14) | 12 (5-19) |
| 5 | 13 (9-18) | 5 (2-11) | 8 (2-14) |

Abbreviation:

TTFields, tumor-treating fields.

* Survival rates are actuarial estimates according to the Kaplan-Meier method.

Figure 3. Overall Survival for Each Prognostic Patient Subgroup of Patients Treated With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone

| Subgroup | TTFields + Temozolomide | | Temozolomide Alone | | Median Survival (IQR), mo | | Hazard Ratio (95% CI) | Favors TTFields + Temozolomide | Favors Temozolomide Alone |
|------------------------------------------------|----------------------------|-------------------------------------|-----------------------|-------------------------------------|----------------------------|-----------------------|--------------------------|--------------------------------------|---------------------------------|
| | No. of Patients | No. (%) Alive at End of Study | No. of Patients | No. (%) Alive at End of Study | TTFields + Temozolomide | Temozolomide Alone | | | |
| MGMT promoter region methylation status | | | | | | | | | |
| Unmethylated | 209 | 18 (9) | 95 | 3 (3) | 16.9 (9.7-28.2) | 14.7 (9.8-24.8) | 0.66 (0.49-0.88) | — | — |
| Methylated | 137 | 26 (19) | 77 | 9 (12) | 31.6 (21.1-48.5) | 21.2 (12.3-37.9) | 0.62 (0.44-0.88) | — | — |
| Resection | | | | | | | | | |
| Biopsy | 60 | 5 (8) | 29 | 0 (0) | 16.5 (9.0-24.7) | 11.6 (7.1-18.1) | 0.50 (0.30-0.84) | — | — |
| Partial | 157 | 20 (13) | 77 | 3 (4) | 21.4 (9.9-37.8) | 15.1 (7.8-23.3) | 0.56 (0.41-0.77) | — | — |
| Gross total | 249 | 32 (13) | 123 | 13 (11) | 22.6 (13.4-39.8) | 18.5 (12.1-31.6) | 0.70 (0.54-0.91) | — | — |
| Region | | | | | | | | | |
| Outside United States | 245 | 32 (13) | 111 | 9 (8) | 20.1 (11.3-32.2) | 15.5 (9.3-25.6) | 0.66 (0.51-0.85) | — | — |
| United States | 221 | 25 (11) | 118 | 7 (6) | 22.0 (11.3-48.2) | 17.1 (9.8-29.2) | 0.63 (0.49-0.82) | — | — |
| Age, y | | | | | | | | | |
| <65 | 377 | 47 (12) | 184 | 14 (8) | 21.6 (12.0-39.4) | 17.3 (10.6-29.3) | 0.69 (0.57-0.85) | — | — |
| ≥65 | 89 | 10 (11) | 45 | 2 (4) | 17.4 (9.0-31.5) | 13.7 (7.6-24.8) | 0.51 (0.33-0.77) | — | — |
| Karnofsky performance score | | | | | | | | | |
| 90-100 | 308 | 39 (13) | 149 | 11 (7) | 23.3 (13.5-41.9) | 17.8 (11.9-29.3) | 0.70 (0.56-0.87) | — | — |
| ≤80 | 154 | 16 (10) | 74 | 5 (7) | 14.9 (8.4-29.8) | 11.0 (5.7-23.3) | 0.58 (0.45-0.88) | — | — |
| Sex | | | | | | | | | |
| Women | 150 | 21 (14) | 72 | 6 (8) | 24.6 (14.4-48.2) | 18.5 (11.3-27.8) | 0.64 (0.56-0.87) | — | — |
| Men | 316 | 35 (11) | 157 | 10 (6) | 19.1 (10.9-34.1) | 15.6 (8.4-28.5) | 0.63 (0.45-0.88) | — | — |
| Overall | 466 | 57 (12) | 229 | 16 (7) | 20.9 (11.3-37.8) | 16.0 (9.3-27.5) | 0.63 (0.53-0.76) | — | — |

Data points represent Cox hazard ratios of overall survival in each subgroup of patients treated with tumor-treating fields (TTFields) plus temozolomide compared with temozolomide alone and were adjusted for the other subgroups. Error bars represent 95% CIs of the hazard ratios. The Karnofsky performance score is measured from 0 to 100 in 10-point increments, with higher scores indicating better patient performance status.

IQR, indicates interquartile range; MGMT, O⁶-methylguanine-DNA methyltransferase promoter region methylation status.

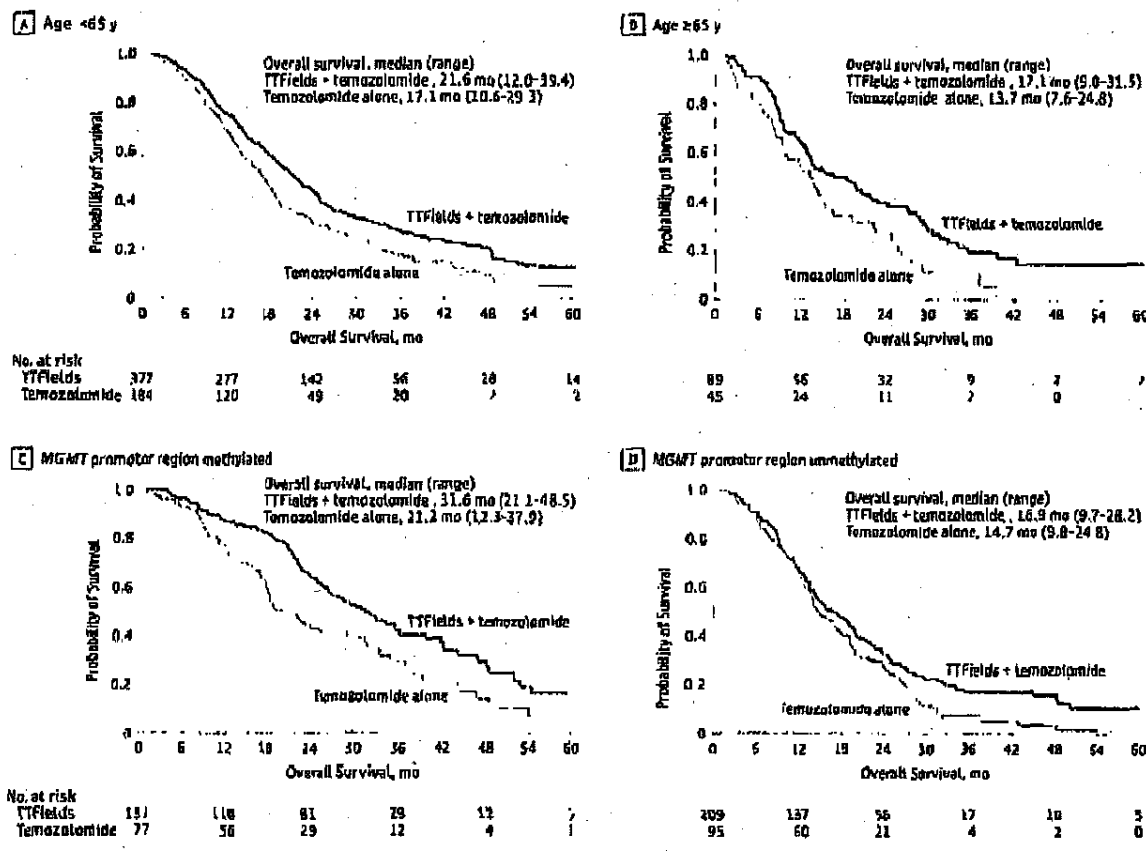
associated with a significant difference in survival ($P = .101$ and $P = .183$, respectively).

Post Hoc Subgroup Analysis

In post hoc analyses, TTFields plus temozolomide was associated with an increase in progression-free survival and overall survival (Figure 3; Cox proportional hazards, $P < .05$ for the treatment effect within each subgroup) in all subgroups of

patients regardless of age, sex, Karnofsky performance score, MGMT promoter methylation status, geographic region, or extent of resection. Patients 65 years or older had shorter survival than patients younger than 65 years. In both age groups, TTFields plus temozolomide was associated with significantly increased survival compared with temozolomide alone for older (HR, 0.51; 95% CI, 0.33-0.77) and younger patients (HR, 0.67; 95% CI, 0.55-0.82; Figure 4A and Figure 4B).

Figure 4. Overall Survival by Patient Age and by MGMT Promoter Region Methylation Status



A, In comparing tumor-treating fields (TTFields) plus temozolomide vs temozolomide alone among patients younger than 65 years the hazard ratio (HR) was 0.67 (95% CI, 0.55-0.82). B, In comparing the 2 treatments among patients 65 years or older, the HR was 0.51 (95% CI, 0.22-0.77). C, In comparing the treatments among patients with MGMT-methylguanine-DNA methyltransferase

MGMT promoter region methylation, the HR was 0.62 (95% CI, 0.43-0.88). D, In comparing the treatments among patients without the MGMT promoter region methylation, the HR was 0.66 (95% CI, 0.49-0.85). The median follow-up of patients was 44 months (range, 25-91 months) in all groups.

Patients with tumors that lacked MGMT promoter methylation had a significantly shorter survival than patients with tumors with MGMT promoter methylation, although use of TTFields with temozolomide was associated with longer survival (HR, 0.66; 95% CI, 0.49-0.85 both in patients with tumors that were MGMT methylated and tumors that were unmethylated, respectively; Figure 4C and Figure 4D). In the TTFields plus temozolomide group, 265 patients who were treated with TTFields for 18 hours a day or more (monthly average in the first 6 months of treatment) had longer survival than 185 patients treated less than 18 hours a day (22.6 months, 95% CI, 19.7-25.1 months vs 19.1 months, 95% CI, 16.5-21.9; HR, 0.65; 95% CI, 0.49-0.85; $P = .009$).

Adverse Events and Tolerability

The addition of TTFields to temozolomide therapy was not associated with any significant increase in rates of systemic adverse events compared with temozolomide therapy alone (48% vs 44%, respectively; $P = .58$; Table 3), and the overall incidence,

distribution, and severity of adverse events were not statistically different in patients in the 2 treatment groups. The numerically higher incidence of some adverse events in the TTFields plus temozolomide group was a reflection of the longer duration of temozolomide treatment in this group due to delayed occurrence of progression. When adverse event incidence normalized to duration of treatment was analyzed, these differences disappeared. The only exception was a higher incidence of localized skin toxic effects (medical device site reaction beneath the transducer arrays) in patients treated with TTFields plus temozolomide; mild to moderate skin irritation was observed in 52% of patients, and severe (grade 3) skin involvement occurred in 2%. Anxiety, confusion, insomnia, and headaches which were reported more frequently (statistically nonsignificant) in patients treated with TTFields at the interim analysis were not seen in the final adverse event analysis of the trial. The incidence of seizures was identical in the 2 groups.

To estimate tolerability, prespecified exploratory analyses of the association of TTFields device use with patients'

Table 3. Adverse Events by Body System and Severity (≥5% Incidence in Any Group)

| ≥1 Adverse event | Grade 3-4 Events, No. (%) of Patients | |
|------------------------------------------------------------------------------------------------------------|------------------------------------------|------------------------------------|
| | TTFIELDS + Temozolomide (n = 456) | Temozolomide Alone (n = 229) |
| Blood and lymphatic system disorders* | 59 (13) | 23 (11) |
| Thrombocytopenia | 39 (9) | 11 (5) |
| Gastrointestinal disorders | 23 (5) | 8 (4) |
| Asthenia, fatigue, and gait disturbance | 42 (9) | 13 (6) |
| Infections | 32 (7) | 10 (5) |
| Injury, poisoning, and procedural complications (falls and medical device site reaction) | 24 (5) | 7 (3) |
| Metabolism and nutrition disorders (anorexia, dehydration, and hyperglycemia) | 16 (4) | 10 (5) |
| Musculoskeletal and connective tissue disorders | 21 (5) | 9 (4) |
| Nervous system disorders | 109 (24) | 43 (20) |
| Seizures | 26 (6) | 13 (6) |
| Respiratory, thoracic and mediastinal disorders (pulmonary embolism, dyspnea, and aspiration pneumonia) | 24 (5) | 11 (5) |

Abbreviation:
TTFIELDS, tumor-treating fields.
* The numerically slightly higher incidence of hematological toxicity, fatigue, and some other adverse effects are due to the longer treatment duration and observation time in the experimental group. The differences disappear when data are normalized to treatment duration.

activities of daily life and cognition were performed using the Karnofsky performance score and the Mini-Mental State Examination. Time to a sustained 6-point decline in the Mini-Mental State Examination score was significantly longer in the TTFIELDS plus temozolomide group than the temozolomide-alone group (16.7 months, 95% CI, 14.7-19.0 months vs 14.2 months, 95% CI, 12.7-17.0 months, respectively; HR, 0.79; 95% CI, 0.66-0.95; $P = .01$). Time to a sustained 10-point decrease in Karnofsky performance score was also significantly longer in the TTFIELDS plus temozolomide group than in the temozolomide-alone group (5.5 months, 95% CI, 5.0-6.3 months vs 3.9 months, 95% CI, 3.1-5.2 months, respectively; HR, 0.80; 95% CI, 0.67-0.95; $P = .009$).

Discussion

In the final analysis of this randomized phase 3 trial, the addition of the TTFIELDS treatment to standard temozolomide maintenance therapy, compared with standard temozolomide maintenance therapy alone, resulted in increased progression-free survival and overall survival in patients with newly diagnosed glioblastoma. After a median follow-up of 40 months, the addition of TTFIELDS to temozolomide, compared with temozolomide alone, resulted in longer median progression-free survival from the time of randomization, 6.7 months vs 4.0 months and longer median overall survival from randomization, 20.9 months vs 16.0 months, respectively. These findings are consistent with the preliminary results reported based on a planned interim analysis of the first 315 patients enrolled, after a median follow-up of 38 months, in which median progression-free survival in the intent-to-treat population was 7.1 months (95% CI, 5.9-8.2 months) in the TTFIELDS plus temozolomide group (210 patients analyzed) and 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide-alone group (105 patients analyzed).

In the current study, exploratory end points were consistent with the primary and secondary end points in this trial. In a post hoc analysis the effect of TTFIELDS was observed in all clinical and molecular subgroups, including patients older than age 65 years and patients with *MGMT* unmethylated tumors.

To assess whether the improved outcome may have been related to other factors than the TTFIELDS therapy the data were scrutinized for possible imbalances, unexpected poor performance of the control group, or differences in supportive care administered to patients between the 2 groups. Both clinical factors and molecular tumor characteristics were well balanced and comparable between the 2 groups. *MGMT* promoter methylation, the strongest predictive factor for outcome in temozolomide-treated patients,²⁸ was more prevalent in the control group (45% vs 40% of samples with a valid result). Patients with early tumor progression occurring during the first 3 months after diagnosis were not included in this trial, and so the randomized patient population had a better prognosis, for both groups, compared with other trials that had randomized patients before radiation therapy. The reported survival times were measured from randomization, not from diagnosis, so for an estimation of the overall outcome 3.8 months should be added in both groups. The RTOG 0525/Intergroup study, which evaluated dose-dense temozolomide, also randomized patients only after completion of radiochemotherapy.⁸ Outcome of the control group in the current study and of the RTOG study were very similar, and in both studies, the median survival from randomization was 16 months.

In this trial, the rates of systemic adverse effects were not significantly different in the 2 treatment groups. The occurrence of mild to moderate skin irritation related to reaction beneath the transducer arrays of the device occurred in more than half of patients in the TTFIELDS plus temozolomide group.

These findings are in contrast to the more than 23 randomized trials conducted over the last decade that have evaluated novel agents or intensified treatment strategies

(eg, dose-dense temozolomide, cilengitide, nimotuzumab, bevacizumab, and rindopepimut^{1,5,8,29}) for treatment of patients with newly diagnosed glioblastoma and have failed to demonstrate improved survival. Innovative treatments for glioblastoma are needed.

Limitations

This study has several limitations. First, the current trial was open-label because it was considered practically unfeasible (heat and easy measure of current associated with TTFields) and ethically unacceptable to expose patients to a sham device. Although a placebo effect may affect subjective end points like quality of life or even progression-free survival by influencing the frequency of imaging and its interpretation, in the current trial a consistent benefit was observed in progression-free survival as assessed by blinded central radiology review, as well as in the gold standard of objective outcome, overall survival. Second, delivery of TTFields therapy requires the patient to continuously carry a device on a

shaved scalp and may create burdens for patients. Nevertheless, the majority of patients were able to handle the device independently or with some help from a caregiver. The fact that 75% of patients achieved treatment adherence of 75% or more (ie, using the device for ≥18 hours per day) indicated good tolerability. The effects of the TTFields treatment and the need for continuous use of the device on quality of life will be reported separately.

Conclusions

In the final analysis of this randomized clinical trial of patients with glioblastoma who had received standard radiochemotherapy, the addition of TTFields to maintenance temozolomide chemotherapy vs maintenance temozolomide alone, resulted in statistically significant improvement in progression-free survival and overall survival. These results are consistent with the previous interim analysis.

ARTICLE INFORMATION

Accepted for Publication: November 9, 2017.

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Author Contributions: Drs Stupp, Ram, and Kirsan had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. **Concept and design:** Stupp, Lieberman, Kirsan, Paki, Ram.

Acquisition, analysis, or interpretation of data: Stupp, Taillibert, Kanner, Read, Steinberg, Lhermitte, Toms, Ididash, Ahluwalia, Fink, Di Meco, Lieberman, Zhu, Stragiolotto, Tran, Bren, Hottinger, Kirsan, Lavy-Shahaf, Weinberg, Kim, Paki, Nicholas, Bruna, Hirte, Weller, Hegi, Ram. **Drafting of the manuscript:** Stupp, Steinberg, Hottinger, Kirsan, Lavy-Shahaf, Ram. **Critical revision of the manuscript for important intellectual content:** Stupp, Taillibert, Kanner, Read, Lhermitte, Toms, Ididash, Ahluwalia, Fink, Di Meco, Lieberman, Zhu, Stragiolotto, Tran, Bren, Hottinger, Kirsan, Weinberg, Kim, Paki, Nicholas, Bruna, Hirte, Weller, Paki, Hegi, Ram. **Statistical analysis:** Steinberg, Kirsan, Lavy-Shahaf. **Obtained funding:** Kirsan, Paki. **Administrative, technical, or material support:** Stupp, Taillibert, Kanner, Read, Toms, Di Meco, Tran, Weinberg, Kim, Paki, Nicholas, Bruna, Weller, Paki. **Supervision:** Stupp, Ahluwalia, Di Meco, Bren, Kirsan, Paki, Bruna, Weller, Ram.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE form for Disclosure of Potential Conflicts of Interest. Dr Stupp reports fees paid to his institution for serving on advisory boards of Celgene, Novartis, AbbVie, and Merck KGaA (Darmstadt) and travel support from Novocure and that his spouse works full time for Celgene. Dr Taillibert reports that she receives fees for patients in clinical trials from the CRNO private foundation of the neurology department in Salpêtrière Hospital. Dr Steinberg reports receiving serving as a statistical consultant for Novocure. Dr Toms reports receiving honoraria for serving on the strategic advisory board and lecturing for Novocure. Dr Ididash reports receiving research support from Foundation ARC, Beta-Innov, and Carthera; travel support from Hoffmann-La Roche and Carthera; serving on the editorial advisory board of *Lettre du Cancérologue*; serving on the advisory boards of Bristol-Myers Squibb and Hoffmann-La Roche; and receiving personal fees from Cipla. Dr Ahluwalia reports receiving grant support, personal fees, or both from Montera Medical, AbbVie, Bristol-Myers Squibb, AstraZeneca, Datar Genetics, CBT Pharmaceuticals, Kadmon Pharmaceuticals, Elsevier, Novocure,

Novartis, Incyte, Pharmacyclics, Tracoe Pharmaceuticals, Prime Oncology, and Carls Lifesciences. Dr Fink reports serving in the speakers program for Genentech and receiving personal fees from Novocure and UCB Pharma. Dr Lieberman reports receiving grant support from Novocure, Stemline, and Roche. Dr Zhu reports receiving grant support from Novocure, Immuno-Cellular Therapeutics, Diffusion Pharmaceuticals LLC, OEK-TEC Inc, NRG Oncology/Radiation Therapy Oncology Group/National Cancer Institute, Boston Biomedical, Summito Calinippon Pharma Global Oncology, Five Prime Therapeutics, Tocagen Inc, and Northwest Biotherapeutics. Dr Tran reports receiving grant support from Merck, Novartis, Northwest Biotherapeutics, Stemline, VBI Therapeutics, and Tocagen, receiving personal fees from Montera, and serving on the advisory board of Novocure. Dr Hottinger reports receiving institutional grant support from Novocure and fees paid to his institution for serving on the advisory boards of Servier and Bristol-Myers Squibb. Dr Kirsan reports that he is an employee of and owns stock in Novocure Ltd, or Weinberg reports that he is an employee of and owns stock in Novocure Ltd. Dr Lavy-Shahaf reports that he is an employee of and owns stock in Novocure Ltd. Dr Hegi reports receiving grant support or personal fees from Novocure, Acceleron, Actelion, Bayer, MSD, Merck EMD, Novocure, OGDZ Pharma, Picur, Roche, Tragara, AbbVie, Bristol-Myers Squibb, Celldex, Pfizer, Progenics, Tava, Tocagen, and Orbus. Dr Paki reports serving as a consultant for, owning stock in, and having pending patents licensed through Novocure. Dr Weller reports receiving financial support from Novocure, serving as an adviser to Bristol-Myers Squibb, and receiving nonfinancial support from MDx-Health. Dr Ram reports that he is a paid consultant for and owns stock in Novocure. No other disclosures were reported.

Funding/Support: The study was funded by Novocure Ltd.

Role of the Funder/Sponsor: Novocure Ltd had a role in the design and conduct of the study; collection, management, and analysis of the data; and decision to submit the manuscript for publication. The study was designed by Drs Stupp

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Research: Clinical Investigation

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JAMA December 19, 2017 Volume 318, Number 23

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Preliminary Communication

Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma A Randomized Clinical Trial

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Reprinted Article from: Volume 314, Number 23 | Pages 2535-2543 | December 15, 2015



A JAMA NETWORK
PUBLICATION

Research

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IMPORTANCE Glioblastoma is the most devastating primary malignancy of the central nervous system in adults. Most patients die within 1 to 2 years of diagnosis. Tumor-treating fields (TTFields) are a locoregionally delivered antimitotic treatment that interferes with cell division and organelle assembly.

OBJECTIVE To evaluate the efficacy and safety of TTFields used in combination with temozolomide maintenance treatment after chemoradiation therapy for patients with glioblastoma.

DESIGN, SETTING, AND PARTICIPANTS After completion of chemoradiotherapy, patients with glioblastoma were randomized (2:1) to receive maintenance treatment with either TTFields plus temozolomide (n = 466) or temozolomide alone (n = 229) (median time from diagnosis to randomization, 3.8 months in both groups). The study enrolled 695 of the planned 700 patients between July 2009 and November 2014 at 83 centers in the United States, Canada, Europe, Israel, and South Korea. The trial was terminated based on the results of this planned interim analysis.

INTERVENTIONS Treatment with TTFields was delivered continuously (>18 hours/day) via 4 transducer arrays placed on the shaved scalp and connected to a portable medical device. Temozolomide (150-200 mg/m²/d) was given for 5 days of each 28-day cycle.

MAIN RESULTS AND MEASURES The primary end point was progression-free survival in the intent-to-treat population (significance threshold of .01) with overall survival in the per-protocol population (n = 280) as a powered secondary end point (significance threshold of .006). This prespecified interim analysis was to be conducted on the first 315 patients after at least 18 months of follow-up.

RESULTS The interim analysis included 210 patients randomized to TTFields plus temozolomide and 105 randomized to temozolomide alone, and was conducted at a median follow-up of 38 months (range, 18-60 months). Median progression-free survival in the intent-to-treat population was 7.1 months (95% CI, 5.9-8.2 months) in the TTFields plus temozolomide group and 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide alone group (hazard ratio [HR], 0.62 [98.7% CI, 0.43-0.89]; P = .001). Median overall survival in the per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the TTFields plus temozolomide group (n = 196) and 15.6 months (95% CI, 13.3-19.1 months) in the temozolomide alone group (n = 84) (HR, 0.64 [99.4% CI, 0.42-0.98]; P = .004).

CONCLUSIONS AND RELEVANCE In this interim analysis of 315 patients with glioblastoma who had completed standard chemoradiation therapy, adding TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00916409

JAMA. 2015;314(23):2535-2543. doi:10.1001/jama.2015.16689

Editorial page 2511

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JR SCRF50A0716

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EXHIBIT 1, PAGE 72

Glioblastoma is the most devastating primary malignancy of the central nervous system in adults. Standard treatment consists of maximal safe surgical resection or a diagnostic biopsy, followed by radiotherapy (60 Gy) with concomitant daily temozolomide chemotherapy, and then maintenance treatment with temozolomide for 6 to 12 months.¹ However, most patients will die within 1 to 2 years. Median progression-free survival from diagnosis of 6.2 to 7.5 months and median overall survival from diagnosis of 14.6 to 16.7 months have been reported in clinical trials.¹⁻⁴ The reported 2- and 5-year survival rates⁵ are 27% and 10%, respectively. During the last decade, all attempts to improve the outcome for patients with glioblastoma have failed when evaluated in large randomized trials.^{2-4,6,7}

Tumor-treating fields (TTFields) are an antimitotic treatment that selectively disrupts the division of cells by delivering low-intensity, intermediate-frequency (200 kHz) alternating electric fields via transducer arrays applied to the shaved scalp.⁸⁻¹⁰ In preclinical models, TTFields have been shown to cause mitotic arrest and apoptosis by disrupting mitotic spindle formation during metaphase and causing dielectrophoretic movement of polar molecules during cytokinesis.^{8,10-12} In a randomized phase 3 trial in which TTFields were compared with chemotherapy in 237 patients with recurrent glioblastoma, the use of TTFields did not prolong progression-free survival or overall survival, but the therapy was associated with better quality of life without the typical chemotherapy-associated toxic effects.¹³

Based on preclinical data demonstrating a synergistic antitumor effect with chemotherapy and TTFields, and pilot clinical feasibility data in combination with temozolomide,⁹ we initiated this phase 3 trial. The objective was to evaluate the efficacy and safety of TTFields used in combination with maintenance temozolomide in patients with glioblastoma after initial treatment with temozolomide and radiotherapy.

Methods

Study Population

Patients eligible for this study (1) had histologically confirmed supratentorial glioblastoma (World Health Organization grade IV astrocytoma¹⁴), (2) were progression-free after having undergone maximal safe debulking surgery when feasible or biopsy, and (3) had completed standard concomitant chemoradiotherapy with temozolomide. Other eligibility criteria were (1) age of 18 years or older, (2) Karnofsky Performance Status (KPS) score of 70% or higher (the KPS score describes the general condition of a patient; a KPS score $\geq 70\%$ ensures some independence in activities of daily living), and (3) adequate bone marrow, liver, and renal function.

Prior use of implanted carmustine wafers was allowed. Patients with infratentorial tumor location and severe comorbidities were excluded. All patients provided written informed consent before entering the study; the study was approved by the institutional review boards or ethics committees of all 83 participating centers. The trial protocol appears in Supplement 1.

Study Design and Treatment

This multicenter, open-label, randomized phase 3 trial was designed to test the efficacy and safety of TTFields in combination with temozolomide for treatment of glioblastoma after initial treatment with chemoradiation. After the completion of treatment with temozolomide and radiotherapy, patients were randomized at a ratio of 2 to 1 (Figure 1) to receive standard maintenance temozolomide chemotherapy (150-200 mg/m²/d for 5 days every 28 days for 6-12 cycles according to the protocol¹ from the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group) with or without the addition of TTFields. Treatment with TTFields was to be initiated within 4 to 7 weeks from the last dose of concomitant temozolomide and radiotherapy. Randomization was performed through a central web-based randomization system and was stratified by extent of resection (biopsy, partial resection, gross total resection) and by O⁶-methylguanine-DNA methyltransferase (MGMT) methylation status (methylated, unmethylated, or unknown).

For patients with available paraffin-embedded tumor tissue, evaluation of MGMT gene promoter methylation status was performed as described previously^{7,15,16} by a central laboratory blinded to treatment group (MDxHealth). If MGMT methylation status could not be determined centrally prior to randomization, local MGMT methylation status was used for stratification.

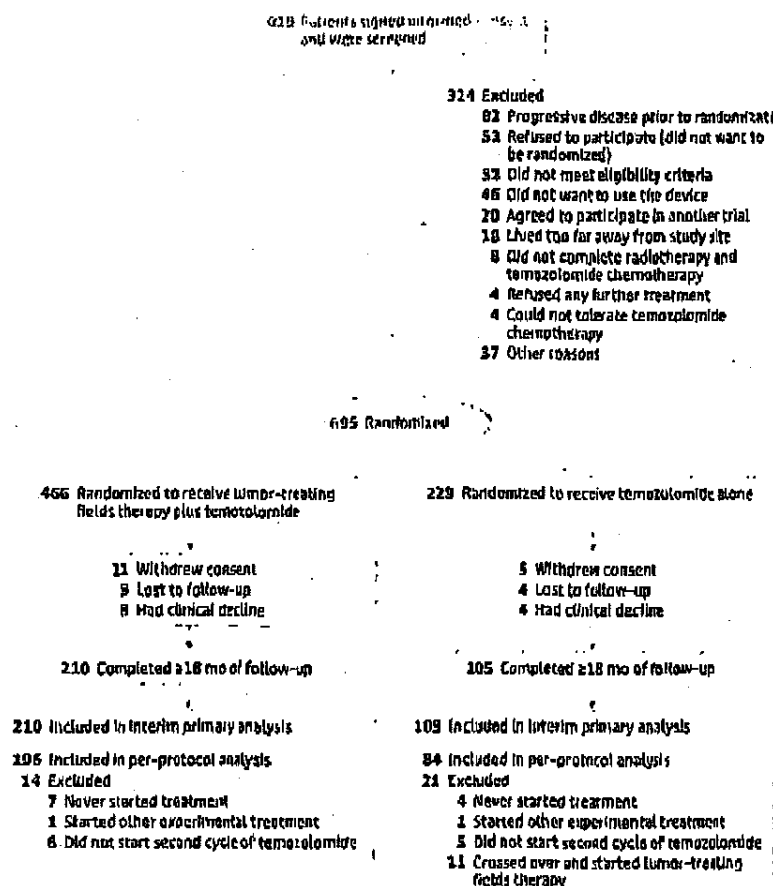
Patients in the TTFields plus temozolomide group received continuous TTFields combined with standard maintenance temozolomide. Patients receiving TTFields had 4 transducer arrays placed on the shaved scalp and connected to a portable device set to generate 200-kHz electric fields within the brain (Optune, Novocure Ltd). Transducer array layouts were determined using a mapping software system for TTFields to optimize field intensity within the treated tumor (NovoTAL, Novocure Ltd). After being trained to operate the device, the patient continued treatment at home. The transducer arrays were supplied in sterile packaging and replaced by the patient, a caregiver, or a device technician twice per week. Although uninterrupted treatment was recommended, short treatment breaks for personal needs were allowed.

If a patient experienced tumor progression, second-line chemotherapy was offered per local practice. However, in the TTFields plus temozolomide group, TTFields could be continued until the second radiological progression, or clinical deterioration, for a maximum of 24 months.

Patient Surveillance and Follow-up

Baseline contrast-enhanced magnetic resonance imaging (MRI) of the brain was required within 2 weeks before starting treatment with maintenance temozolomide with or without TTFields. A complete physical examination with collection of laboratory parameters was performed within 1 week of treatment initiation. The evaluation also included a quality-of-life questionnaire (QLQ-C30) that has a brain-specific module (BN-20), which was developed by the European Organisation

Figure 1. Recruitment and Inclusion of Patients in the Study



for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups.^{17,18} A Mini-Mental State Examination (a short bedside test used to evaluate cognition and memory) also was administered (a test result of 27-30 points is considered normal function).

Patients were seen monthly for medical follow-up and routine laboratory examinations. Quality of life was assessed every 3 months. Magnetic resonance imaging was to be performed every second month after the baseline MRI until second radiological progression in all patients. In the event of clinical progression, MRI was to be performed within 1 week after the study investigator became aware of it. All MRIs were reviewed centrally by 2 blinded independent radiologists (BioClinica Inc) and were evaluated for tumor response and progression using the criteria developed by Macdonald et al.¹⁹ In cases in which the central reviewers were not in agreement, a third blinded radiologist adjudicated between them. The third radiologist was involved in 17% of the cases in the TTF fields plus temozolomide group and in 18% of the cases in the temozolomide alone group.

The results of the central review were not communicated to the study investigator, and all treatment decisions were based on local imaging interpretation. Eight patients in the

TTF fields plus temozolomide group (4%) compared with 6 patients in the temozolomide alone group (3%) were considered stable by blinded central review; however, treatment had been changed by the study investigator due to local interpretation of tumor progression. Patients were removed from the progression-free survival analysis at the date of treatment change when this occurred before evidence of tumor progression or when patients reached the cutoff date without tumor progression.

Adverse events were recorded prospectively according to the National Cancer Institute's Common Terminology Criteria (version 3.0) until 2 months after treatment discontinuation. Adverse events are presented descriptively as number and percentage of patients with each adverse event term for all patients available at the time of the interim analysis. Treatment adherence with TTF fields was recorded electronically by the device as average daily use in hours per day and information was reviewed and transferred at the monthly follow-up visit.

Statistical Considerations

The primary end point was progression-free survival in the intent-to-treat (ITT) population assessed by an independent review panel (80% power; hazard ratio [HR], 0.78; 2-sided α level

of .05). The study was also designed to have 80% power (HR, 0.76; 2-sided α level of .05) to examine overall survival as a secondary end point. To avoid an increase in the risk of a false-positive result, overall survival was to be tested statistically only if the primary end point was met.

This prespecified interim analysis was to be performed after the first 315 randomized patients reached a minimum 18-month follow-up. The final type I error rate of 0.05 was split between the interim and final analyses based on a standard spending function.²⁰⁻²² The protocol prespecified that overall survival would be analyzed in an as-treated population, excluding all patients in both treatment groups who (1) never started maintenance temozolomide, (2) had major protocol violations, (3) crossed over to the other treatment group, or (4) received TTFIELDS outside the protocol setting.

The primary end point would be achieved in the interim analysis if progression-free survival in the ITT population was significantly longer in the intervention group compared with the control group using a stratified log-rank test with an α level of .01. The secondary end point would be achieved in the interim analysis if overall survival in the as-treated population (per-protocol population) was significantly longer in the TTFIELDS plus temozolomide group using a stratified log-rank test with an α level of .006. The confidence intervals that go with the HRs are presented as 1 minus the prespecified α level for each analysis. For example, the α level in the per-protocol interim analysis for overall survival was .006. Therefore, the corresponding confidence interval used for presenting the HRs was 1.000 - 0.006 (99.4% confidence interval). An upper confidence limit of less than 1 indicates the prespecified statistical threshold was met. An independent data and safety monitoring committee was chartered to stop the trial if the interim analysis of progression-free survival (ITT population) and overall survival (per-protocol population) surpassed these predetermined thresholds, as well as for futility or safety concerns.

In addition to these prespecified analyses, an analysis of overall survival in the ITT population was performed. Furthermore, a robustness analysis including all 695 patients enrolled in the trial served to validate the findings of the interim analysis (database lock: December 29, 2014; eAppendix 1 in Supplement 2).

Multiple imputation analyses also were performed for the trial's primary end point of progression-free survival in the ITT population to test the sensitivity of the results to possible bias using informative and interval censoring. These analyses included (1) treating all patients with informative censoring as treatment failures in the TTFIELDS plus temozolomide group, (2) censoring all patients with informative censoring in the temozolomide alone group (worst case scenario), and (3) treating all events in the TTFIELDS plus temozolomide group and in the temozolomide alone group as occurring differentially at different periods during the inter-MRI interval before the date of tumor progression.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) and R version 3.1.1.²³ The final analysis will be performed when all 695 patients enrolled in the study have at least 18 months of follow-up and will include prespec-

fied subgroup analyses and additional secondary end points, including quality of life.

Results

Study Participants

Between July 2009 and November 2014, there were 695 patients with newly diagnosed glioblastoma randomized to receive either TTFIELDS plus temozolomide ($n = 466$) or temozolomide alone ($n = 229$). Data for the interim analysis included 210 patients randomized to TTFIELDS plus temozolomide and 105 to temozolomide alone (Figure 1; database lock: September 5, 2014). The independent data and safety monitoring committee met in October 2014 to review the interim analysis; the trial met the predefined boundaries for success (improvement of both progression-free and overall survival) and the committee recommended study termination, thus allowing patients in the control group to crossover and receive TTFIELDS.

After approval of study termination by the US Food and Drug Administration, the trial was closed to recruitment on November 29, 2014, after 695 patients of the planned 700 patients had already been randomized. All patients in the control group with ongoing maintenance therapy were offered to receive TTFIELDS. At the time of this report, 35 patients in the control group crossed over to receive TTFIELDS. Follow-up for all patients continues according to the protocol.

Patient baseline characteristics were well balanced between the 2 groups (Table 1). The median age was 57 years and 66% were male. The median KPS score was 90%. Sixty-four percent of patients had a gross total resection and 11% had only a diagnostic biopsy. Tumor tissue for central MGMT testing was available for 72% of the patients; the MGMT methylation frequency was 39% (75/191 valid tests; 39% for the TTFIELDS plus temozolomide group and 41% for the temozolomide alone group). Tumor location in the brain was also comparable.

Garnustine wafers (Gliadel) were used at initial surgery in 2.4% of patients in the TTFIELDS plus temozolomide group vs 2.9% of patients in the temozolomide alone group. Ninety-five percent of the patients were white and 61% were treated in the United States. The rest of the patients were treated at centers in Canada, Europe, Israel, and South Korea. The median time from diagnosis to randomization was 3.8 months (range, 2.0-5.7 months) for patients in the TTFIELDS plus temozolomide group and 3.8 months (range, 1.4-5.7 months) for those in the temozolomide alone group. The median time from the end of treatment with temozolomide and radiotherapy to randomization was 36 days in the TTFIELDS plus temozolomide group and 38 days in the temozolomide alone group; 53% of patients were randomized after having started the first cycle of maintenance temozolomide. The median time from randomization to initiation of TTFIELDS was 5 days.

Treatment Delivery

All patients had completed radiotherapy and concomitant temozolomide as per local practice. The median number of temozolomide cycles until evidence of first tumor progression was 6 cycles (range, 1-26 cycles) for patients in the TTFIELDS

Table 1. Patient Baseline Characteristics and Treatment Details

| | All Patients (N = 315) | TTFelds Plus Temozolomide (n = 210) | Temozolomide Alone (n = 105) |
|-----------------------------------------------------------------------------------------|---------------------------|-------------------------------------------|------------------------------------|
| Age, y | | | |
| Mean (SD) | 55.8 (11.1) | 55.3 (11.3) | 56.8 (10.5) |
| Median (range) | 57 (20-83) | 57 (20-83) | 58 (21-83) |
| Karnofsky Performance Status score, median (range), % ^a | 90 (60-100) | 90 (60-100) | 90 (70-100) |
| Sex, No. (%) | | | |
| Male | 207 (66) | 140 (67) | 67 (64) |
| Female | 108 (34) | 70 (33) | 38 (36) |
| Use at baseline, No. (%) | | | |
| Antiepileptic medication | 126 (40) | 88 (42) | 38 (36) |
| Corticosteroid therapy | 77 (24) | 51 (24) | 26 (25) |
| Mini-Mental State Examination score, No. (%) ^b | | | |
| ≤26 | 45 (15) | 31 (15) | 14 (13) |
| 27-30 | 247 (78) | 174 (83) | 73 (70) |
| Unknown | 23 (7) | 5 (2) | 18 (17) |
| Extent of resection, No. (%) | | | |
| Gross total resection | 34 (11) | 23 (11) | 11 (10) |
| Partial resection | 79 (25) | 52 (25) | 27 (26) |
| Gross total resection | 202 (64) | 135 (64) | 67 (64) |
| Tissue available and tested, No. (%) | 227 (72) | 152 (72) | 75 (71) |
| MGMT methylation | 75 (33) | 49 (32) | 26 (35) |
| No methylation | 116 (51) | 79 (52) | 38 (51) |
| Invalid test result | 36 (16) | 24 (16) | 11 (15) |
| Region, No. (%) | | | |
| United States | 191 (61) | 127 (60) | 64 (61) |
| Rest of world | 124 (39) | 83 (40) | 41 (39) |
| Completed radiation therapy, No. (%) | | | |
| <57 Gy | 18 (6) | 13 (6) | 5 (5) |
| 60 Gy (standard; ±5%) | 291 (92) | 191 (91) | 100 (95) |
| >63 Gy | 6 (2) | 6 (3) | 0 (0) |
| Concomitant temozolomide use, No. (%) | | | |
| Yes | 308 (98) | 207 (99) | 101 (96) |
| Unknown | 7 (2) | 3 (1) | 4 (4) |
| Time from event to randomization, median (range), d | | | |
| Last day of radiotherapy | 37 (13-68) | 35 (13-53) | 38 (13-58) |
| Initial diagnosis | 114 (43-171) | 115 (59-171) | 113 (43-170) |
| No. of maintenance temozolomide cycles until first tumor progression, median (range) | 6 (1-26) | 6 (1-26) | 4 (1-24) |
| Duration of treatment with TTFelds, median (range), mo | 9 (1-58) | 9 (1-58) | |
| Adherence to TTFelds therapy ≥75% during first 3 mo of treatment | | 157 (75) | |

Abbreviations: MGMT, O⁶-methylguanine-DNA methyltransferase; TTFelds, tumor-treating fields.

^a A higher score indicates better functional status.

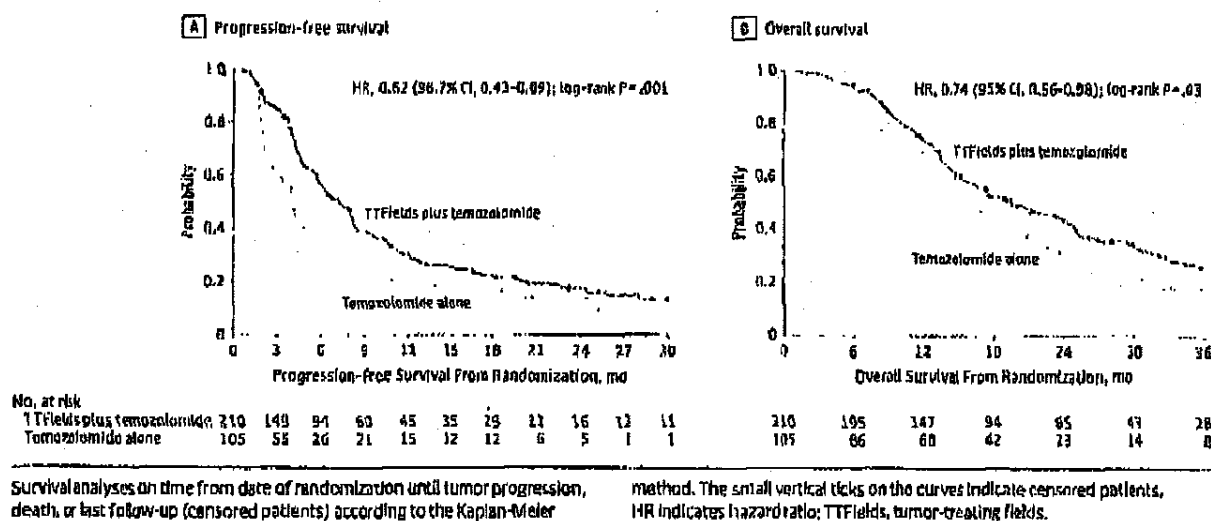
^b A higher score indicates better cognitive capability.

plus temozolomide group and 4.0 cycles (range, 1-24 cycles) for patients in the temozolomide alone group; the median duration of treatment with TTFelds was 9 months (range, 1-58 months). Two-thirds (n = 141) of patients in the TTFelds plus temozolomide group continued treatment with TTFelds after first tumor progression. Three-quarters (n = 157) of patients receiving treatment with TTFelds were adherent to therapy (ie, wearing the device ≥18 hours per day on average during the first 3 treatment months).

Efficacy End Points

As prespecified, the primary end point for the efficacy results was based on progression-free survival in the ITT population of the interim analysis data set. After a median follow-up of 38 months (range, 18-60 months), the median progression-free survival from randomization was 7.1 months (95% CI, 5.9-8.2 months) in the TTFelds plus temozolomide group compared with 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide alone group (HR, 0.62 [98.7% CI, 0.43-0.89];

Figure 2. Survival Curves for Patients Included In the Interim Analysis In the Intent-to-Treat Population



stratified log-rank $P = .001$; Figure 2A). Thus, adding TTFelds to temozolomide treatment increased median progression-free survival in the ITT population by 3.1 months.

As per the statistical analysis plan, overall survival was to be tested in a prespecified per-protocol population only after the primary end point was found to surpass the threshold for significance in the interim analysis. Median overall survival in the per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the TTFelds plus temozolomide group ($n = 196$) compared with 15.6 months (95% CI, 13.3-19.1 months) in the temozolomide alone group ($n = 84$) (HR, 0.64 [95% CI, 0.42-0.98]; stratified log-rank $P = .004$). The details on the per-protocol population and analyses are summarized in eAppendix 2 in Supplement 2.

In additional analyses in the ITT population, the median overall survival was 19.6 months (95% CI, 16.6-24.4 months) in the TTFelds plus temozolomide group compared with 16.6 months (95% CI, 13.6-19.2 months) in the temozolomide alone group (HR, 0.74 [95% CI, 0.56-0.98]; stratified log-rank $P = .03$; Figure 2B). The percentage of patients alive at 2 years following enrollment was 43% in the TTFelds plus temozolomide group and 29% in the temozolomide alone group ($P = .006$).

To assess the robustness of the interim analysis findings, additional analyses on all 695 patients randomized were performed. Patient characteristics of all patients randomized did not differ significantly from the interim data set, and the results for the main end points were similar in these analyses compared with the interim analysis (eAppendix 1 in Supplement 2).

Second-line treatments, such as nitrosoureas, temozolomide rechallenge, and bevacizumab, were received by 67% of the patients in the TTFelds plus temozolomide group compared with 57% in the temozolomide alone group; about 40% of second-line therapies included bevacizumab and about 40% included nitrosoureas. The type of chemotherapy used at recurrence was balanced between treatment groups.

Secondary imputation analyses of progression-free survival with relation to the effects of interval and informational censoring did not change the conclusions of the primary progression-free survival analysis (eAppendix 3 in Supplement 2).

Safety and Tolerability

The addition of TTFelds to temozolomide therapy in patients with newly diagnosed glioblastoma was not associated with any significant increase in systemic toxic effects compared with temozolomide therapy alone (Table 2). The overall incidence, distribution, and severity of adverse events were similar in patients treated with TTFelds plus temozolomide and in those treated with temozolomide alone. The only notable exception was a higher incidence rate of localized skin toxicity (medical device site reaction beneath the transducer arrays) in patients treated with TTFelds plus temozolomide. Mild to moderate skin irritation was observed in 43% of patients treated with TTFelds plus temozolomide and severe skin reaction (grade 3) in 2%. Mild anxiety, confusion, insomnia, and headaches were reported more frequently in the patients treated with TTFelds plus temozolomide and occurred mainly at the time of therapy initiation. The incidence of seizures was almost identical in the 2 groups (15 [7%] in the TTFelds plus temozolomide group vs 8 [8%] in temozolomide alone group). A total of 12 patients died of causes considered unrelated to treatment while receiving adjuvant therapy (8 [3.9%] in the temozolomide plus TTFelds group and 4 [4.0%] in the temozolomide alone group; Table 2).

Discussion

Glioblastoma is a highly aggressive brain tumor affecting men and women, frequently at the peak of life. Prognosis remains poor with no major treatment advance in more than a decade. In the interim analysis of this randomized clinical trial,

the addition of TTFields to standard maintenance temozolomide significantly improved progression-free and overall survival. The prespecified analyses revealed that patients randomized to receive TTFields plus temozolomide compared with patients randomized to receive temozolomide alone had a median progression-free survival of 7.1 months vs 4.0 months (ITT analyses). Patients who received TTFields plus temozolomide had a median overall survival of 20.5 months compared with 15.6 months in those who received temozolomide alone (as per the prespecified per-protocol analysis; the ITT analysis did not differ substantially).

Based on the results of this planned interim analysis, the trial's independent data and safety monitoring committee recommended termination of the trial. Because almost all patients had been enrolled (695/700) in the study by the time the recommendation was implemented, the full trial population will be followed up for both progression-free and overall survival. Subsequent analyses of all secondary end points and subgroups will be performed when the follow-up data are available.

The trial population and the results in the control group in this study were comparable with other glioblastoma clinical trials. Nevertheless, patients in this trial were randomized only after the end of radiochemotherapy, and for most, the first cycle of maintenance temozolomide had been started at the time of randomization; thus, patients with early tumor progression during radiochemotherapy were excluded. Most glioblastoma trials have reported survival from the date of initial diagnosis or study enrollment before starting radiochemotherapy, thus 3 to 4 months before randomization of the current study.

When the interval from diagnosis to randomization is added to the outcome results in this study, the progression-free survival of 7.8 months in the control group is comparable with most other reported studies, and supports the generalizability of these results. The Radiation Therapy Oncology Group (RTOG) 0525 protocol randomized patients only after the end of treatment with temozolomide and radiotherapy, similar to our study.³ The control groups with standard dose temozolomide only in these 2 trials were comparable: progression-free survival from randomization of 4.0 months in the present study and 5.5 months in the RTOG 0525 trial and overall survival of 16.6 months in both trials. Thus, the benefit observed with TTFields cannot be simply attributed to patient selection. In the present trial, the gain of 3 months in both median progression-free survival (from 4.0 months to 7.2 months; HR, 0.62) and median overall survival (from 16.6 months to 19.6 months; HR, 0.74), translating into a survival gain at 2 years of 14% (from 29% to 43%) in the ITT population is in the range of benefit that is considered clinically meaningful for therapeutic agents in oncology.

The prespecified analysis for overall survival in the interim analysis was to be based on the per-protocol population ($n = 280$); ie, removal in both study groups of the patients who did not start their second course of maintenance temozolomide or had major protocol violations. This analysis met the prespecified threshold for efficacy in the interim analysis for the per-protocol population. In a more conserva-

Table 2. Grade 3 to 4 Treatment-Emergent Adverse Events

| | No. (%) of Patients With Adverse Events ^a | |
|--------------------------------------------------|-------------------------------------------------------|-----------------------------------------------|
| | TTFields Plus Temozolomide ($n = 203$) ^b | Temozolomide Alone ($n = 101$) ^c |
| Hematological disorders ^d | 25 (12) | 9 (9) |
| Anemia | 1 (<1) | 2 (2) |
| Leukopenia or lymphopenia | 11 (5) | 5 (5) |
| Neutropenia | 6 (3) | 1 (1) |
| Thrombocytopenia | 19 (9) | 3 (3) |
| Cardiac disorders | 2 (1) | 1 (1) |
| Eye disorders | 2 (1) | 1 (1) |
| Gastrointestinal disorders ^d | 11 (5) | 2 (2) |
| Abdominal pain | 2 (1) | 0 |
| Constipation | 2 (1) | 0 |
| Diarrhea | 1 (<1) | 2 (2) |
| Vomiting | 3 (1) | 1 (1) |
| General disorders | 17 (8) | 5 (5) |
| Fatigue | 8 (4) | 4 (4) |
| Infections | 10 (5) | 3 (3) |
| Injury and procedural complications ^d | 14 (7) | 5 (5) |
| Fall | 6 (3) | 2 (2) |
| Medical device site reaction | 4 (2) | 0 |
| Metabolism and nutrition disorders | 7 (3) | 3 (3) |
| Musculoskeletal disorders | 8 (4) | 3 (3) |
| Nervous system disorders ^d | 45 (22) | 25 (25) |
| Seizure | 15 (7) | 8 (8) |
| Headache | 4 (2) | 2 (2) |
| Psychiatric disorders ^d | 9 (4) | 1 (1) |
| Anxiety | 2 (1) | 0 |
| Bradypnea | 0 | 1 (1) |
| Confusional state | 2 (1) | 1 (1) |
| Mental status changes | 4 (2) | 1 (1) |
| Psychotic disorder | 2 (1) | 0 |
| Respiratory disorders | 4 (2) | 1 (1) |
| Skin disorders | 0 | 1 (1) |
| Vascular disorders ^d | 8 (4) | 8 (8) |
| Deep vein thrombosis | 1 (<1) | 3 (3) |
| Pulmonary embolism | 4 (2) | 5 (5) |

Abbreviation: TTFields, tumor-treating fields.

^a Safety is reported on patients who have received any treatment. Randomized patients who never received any maintenance therapy were excluded from this safety analysis.

^b Eight patients died while receiving adjuvant therapy due to causes unrelated to therapy (1 patient for each of the following reasons: cardiac events, pulmonary emboli, respiratory, and infection; and 4 patients with central nervous system disorders likely due to tumor progression).

^c Four patients died while receiving adjuvant therapy due to causes unrelated to therapy (1 patient for each of the following reasons: cardiac events, pulmonary emboli, respiratory, and unknown).

^d Patients may have had more than 1 adverse event so subcategories do not total and not all events are subcategorized.

tive analysis using the ITT population, an overall survival benefit was also manifest. Furthermore, an analysis of robustness performed on all randomized patients enrolled at the time

of study termination (eAppendix 1 in Supplement 2) supports the conclusions of the interim analysis.

This clinical trial has some important limitations. Patient enrollment occurred only after the end of radiochemotherapy, leading to some variation in the delivery of standard treatment of temozolomide and radiotherapy. Patients who had progressed early during radiochemotherapy were not eligible for randomization, thus excluding patients with very poor prognoses. There is likely reporting bias for second-line therapies after tumor progression because in the TTFields plus temozolomide group, TTFields were to be continued, and thus, more detailed treatment information has been tracked for this group.

This analysis reports a planned interim analysis on data from the first 315 patients with at least 18 months of follow-up; however, for detailed and meaningful subgroup analyses, the mature data of the full data set will be needed. Treatment failure patterns, effects of second-line therapies, and additional molecular analyses on baseline tumor biopsies will allow for better understanding of the clinical effects of this novel treatment modality. With the last patient randomized on November 29, 2014, however, these data are not expected before the end of 2016.

This was an open-labeled study. A sham or placebo treatment for the control group was considered neither practical (patients would be able to sense heat when they were receiving TTFields) nor appropriate (due to the burden for patients and caregivers and the need to shave the scalp and have transducer arrays placed). In this respect, the trial resembles studies evaluating radiation therapy. This raises the question of a placebo effect leading to the improved outcome. Although some effect of placebo may be expected on subjective end points, such as cognitive function and quality of life, objective end points, such as overall and progression-free survival (assessed by a blinded review panel), are independent of pla-

cebo effects in cancer therapy.²⁴ The panel did not have information on treatment received and no stigmata of TTFields array pads were evident on MRI.

Recent randomized studies of patients with glioblastoma, which did not use placebo controls, failed to show any increase in progression-free or overall survival^{2,7} despite intensive treatment regimens requiring twice weekly hospital visits.⁷ The magnitude of effect size seen in the present trial (HR of 0.62 for progression-free survival and 0.74 for overall survival) is beyond what could be attributed to a placebo effect. In addition, the support provided to patients in the TTFields plus temozolomide group by device support specialists during the trial was largely technical in nature and did not include medical supportive care. Medical follow-up with monthly visits was the same for both treatment groups.

Because TTFields were applied only to the head, an increase in systemic adverse events was neither seen nor expected. No increase in seizure rate or neurological adverse events was observed. Almost half of the patients treated with TTFields did experience some grade 1 to 2 (mild to moderate) localized skin reaction related to the application of the transducer arrays used to deliver the TTFields. This adverse effect could be managed using published skin care guidelines for patients receiving TTFields.²⁵ Only 2% of patients receiving TTFields had grade 3 to 4 (severe) skin reactions beneath the transducer arrays.

Conclusions

In this interim analysis of 315 patients with glioblastoma who had completed standard chemoradiation therapy, adding TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival.

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New Jersey Neuroscience Institute, Edison (Landolf); Maine Medical Center, Portland (Desai); Fondazione Ospedale Maggiore Policlinico, Milan, Italy (Cardi); Houston Methodist Hospital, Houston, Texas (Kew); Hospices Civils de Lyon, University Claude Bernard Lyon 1, Lyon, France (Honnorat); Novocure, Haifa, Israel (Kirsan, Weinberg, Palti).

Author Contributions: Drs Stupp and Ram had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Stupp, Kirsan, Weinberg, Palti, Ram.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Stupp, Kirsan, Ram.

Critical revision of the manuscript for important intellectual content: All authors.

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Obtained funding: Palti.

Administrative, technical, or material support:

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Study supervision: Stupp, Kirsan, Weinberg, Hegl, Ram.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for

Disclosure of Potential Conflicts of Interest. Dr Stupp reported receiving travel assistance from Novocure for data review and presentation of the results at medical meetings; and receiving personal fees for serving on advisory boards for Roche/Genentech, Merck KGaA, Merck & Co, and Novartis. Dr Taillibert reported receiving personal fees from Mundipharma EDO and Roche. Dr Kanner reported receiving institutional grant funding and personal fees for speaking and device training from Novocure. Dr Keson reported receiving institutional grant funding and personal fees for consulting and attending advisory meetings from Novocure. Dr Steinberg reported receiving consulting fees from Novocure for performing the statistical analysis. Dr Toms reported receiving personal fees from Novocure for serving on an advisory board. Dr Lieberman reported receiving institutional grant funding from Novocure. Dr Fink reported receiving personal fees from Novocure for serving on an advisory board; and receiving personal fees from Genentech for serving in the speakers program. Dr Zhu reported receiving institutional grant funding and personal fees from Novocure. Dr Engelhard reported receiving institutional grant funding and personal fees from Novocure. Dr Chen reported receiving grant funding, personal fees, nonfinancial support, and being a stock holder and chief

oncology officer in Pharma-kinesis; and receiving grant funding, personal fees, nonfinancial support, and being a stock holder in and CEO of NeoNe Technologies. Dr David Tran reported receiving grant funding from Celldex, INVivoTech, Novocure, and Merck; and receiving personal fees from Novocure and PRIME Oncology. Dr Holtzinger reported receiving travel reimbursement and speakers fees from Novocure and Merck Sharp & Dohme; and receiving personal fees for serving on an advisory board for Roche. Dr Landolfi reported receiving personal fees from Novocure for serving on an advisory board. Dr Honnart reported receiving trial support from Novocure and serving on an advisory board for Novocure. Dr Kibali reported receiving grants from Fondation ARC pour la recherche sur le Cancer; receiving research support from IntactChemos and Beta-Innov; receiving personal fees from Novartis for attending a conference; receiving travel reimbursement from Hoffmann-La Roche; and serving as an editorial advisory board member for *Lettre du Cancérologue*. Drs Kirson, Weinberg, and Palti reported being employees of Novocure. Dr Palti also reported holding 35 issued US patents and minority stock ownership in Novocure. Dr Hegl reported receiving institutional grant funding from Novocure, Merck Sharp & Dohme, Roche, and Merck-Serono; and nonfinancial support from MDxHealth for sample testing. Dr Ram reported receiving institutional grant funding from Novocure; and serving as a paid consultant for and holding stock options in Novocure. Drs Taylor, Silvani, Barnett, Henson, Sroubek, Nam Tran, Desai, Carlini, and Kew reported having no disclosures.

Funding/Support: The study was funded by Novocure Ltd.

Role of the Funder/Sponsor: Novocure Ltd had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The study was designed by the first and last authors (R.S. and Z.R.), together with representatives from Novocure (mainly E.D.K.). The study oversight was supported and monitored by a clinical research organization (CRO), who also holds the database. Data were collected by the investigators and monitored by the CRO. Device use data were downloaded monthly and transferred to the study investigators or their research staff by device support specialists from Novocure Ltd. The data were analyzed separately by the statistician of the independent data monitoring committee and the study statistician (D.M.S.). Data interpretation was the responsibility of the first and last authors (R.S. and Z.R.), together with the study sponsor representative and project lead (E.D.K.). These 3 physicians also jointly developed the first draft. A subsequent mature draft and a prefinal version were circulated among all authors who gave additional input, contributed to, and approved the manuscript. The first and last authors (R.S. and Z.R.) and E.D.K. had full access to all data, and also reviewed all patient profiles for consistency (R.S. and E.D.K.). The decision to publish the data followed the independent data and safety monitoring committee recommendation for data release, and was supported by all coauthors.

The roles of employees of Novocure are described in the respective author contributions. Other employees' involvement was limited to technical support of the device.

Additional Contributions: We thank the patients and their families for participating in the trial. We are grateful to all of the EF-14 investigators, who are listed in Appendix 4 in Supplement 2, and the nursing staff for taking care of the patients.

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Indications For Use and Safety Information in the United States:

Please visit www.optune.com/IFU for Optune Instructions For Use (IFU) for complete information regarding the device's indications, contraindications, warnings and precautions.

Optune is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM).

Optune with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery, and completion of radiation therapy together with concomitant standard of care chemotherapy.

For the treatment of recurrent GBM, Optune is indicated following histologically- or radiologically-confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

Summary of Important Safety Information**Contraindications**

Do not use Optune in patients with an active implanted medical device, a skull defect (such as, missing bone with no replacement), or bullet fragments. Use of Optune together with implanted electronic devices has not been tested and may theoretically lead to malfunctioning of the implanted device. Use of Optune together with skull defects or bullet fragments has not been tested and may possibly lead to tissue damage or render Optune ineffective.

Do not use Optune in patients that are known to be sensitive to conductive hydrogels. In this case, skin contact with the gel used with Optune may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings and Precautions

Optune can only be prescribed by a healthcare provider that has completed the required certification training provided by Novocure (the device manufacturer).

Do not prescribe Optune for patients that are pregnant, you think might be pregnant or are trying to get pregnant, as the safety and effectiveness of Optune in these populations have not been established.

The most common ($\geq 10\%$) adverse events involving Optune in combination with temozolomide were thrombocytopenia, nausea, constipation, vomiting, fatigue, medical device site reaction, headache, convulsions, and depression.

Use of Optune in patients with an inactive implanted medical device in the brain has not been studied for safety and effectiveness, and use of Optune in these patients could lead to tissue damage or lower the chance of Optune being effective.

If the patient has an underlying serious skin condition on the scalp, evaluate whether this may prevent or temporarily interfere with Optune treatment.

Indications for use and safety information in Europe:**Newly diagnosed GBM**

Optune is intended for the treatment of patients with newly diagnosed GBM, after surgery and radiotherapy with adjuvant temozolomide, concomitant to maintenance temozolomide. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after surgery and radiation therapy with adjuvant temozolomide. Treatment may be given together with maintenance temozolomide (according to the prescribing information in the Temodar package insert) and after maintenance temozolomide is stopped.

Recurrent GBM

Optune is intended for the treatment of patients with recurrent GBM who have progressed after surgery, radiotherapy and temozolomide treatment for their primary disease. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after the latest surgery, radiation therapy or chemotherapy.

Contraindications

Do not use Optune if you are pregnant, think you might be pregnant, or are trying to get pregnant. If you are a woman who is able to get pregnant, you must use birth control when using the device. Optune was not tested in pregnant women. Do not use Optune if you have clinically significant hepatic, renal or hematologic disease. Do not use Optune if you have significant additional neurological disease (primary seizure disorder, dementia, progressive degenerative neurological disorder, meningitis or encephalitis, hydrocephalus associated with increased intracranial pressure). Do not use Optune if you are known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the gel used with Optune Treatment Kit may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings and Precautions

Use Optune only after receiving training from qualified personnel, such as your doctor, a nurse, or other medical personnel who have completed a training course given by the device manufacturer (Novocure). All servicing procedures must be performed by qualified and trained personnel.

Do not use Optune Treatment Kit if you are 17 years old or younger. The system has not been tested in persons 17 years old or younger. It is unknown what side effects the device may cause in these cases or if it will be effective.

Do not wet the device or the transducer arrays. Do not use any parts that do not come with the Optune treatment kit, or that were not sent to you by the device manufacturer or given to you by your doctor.

Optune commonly causes skin irritation beneath the transducer arrays and in rare cases lead to headaches, falls, fatigue, muscle twitching or skin ulcers.

For complete information regarding Optune's indication, contraindication, warnings and precautions please see the [Instructions for Use \(IFU\)](http://www.optune.com/ifu). (<http://www.optune.com/ifu>)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

October 05, 2015

Novocure, Ltd.
% Mr. Jonathan S. Kahan
Partner
Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004

Re: P100034/S013
Trade/Device Name: Optune™ (Formerly the NovoTTF-100A System)
Filed: April 10, 2015
Amended: July 23, 2015
Product Code: NZK

Dear Mr. Jonathan S. Kahan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) supplement for the Optune™ (formerly the NovoTTF-100A System). This device is indicated as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy. Optune™ was previously approved in 2011 for the treatment of recurrent GBM with the following Indications for Use (IFU): Optune™ is indicated following histologically-or radiologically-confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted. We are pleased to inform you that the PMA supplement is approved. You may begin commercial distribution of the device as modified in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is

Page 2 – Mr. Jonathan S. Kahan

P100034/S013

therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices:

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84. This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of the final UDI rule. These provisions include the requirement to provide a UDI on the device label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, 21 CFR 814.84 (b)(4) requires PMA annual reports submitted after September 24, 2014, to identify each device identifier currently in use for the subject device, and the device identifiers for devices that have been discontinued since the previous periodic report. It is not necessary to identify any device identifier discontinued prior to December 23, 2013. For more information on these requirements, please see the UDI website, <http://www.fda.gov/udi>.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm>

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

Page 3 – Mr. Jonathan S. Kahan

P100034/S013

1. May have caused or contributed to a death or serious injury; or
2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at <http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm>

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at <http://www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm>

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm>. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in 6 copies, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

Page 4 - Mr. Jonathan S. Kahan

P100034/S013

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Daryl Kaufman at 301-796-6467 or Daryl.Kaufman@fda.hhs.gov.

Sincerely yours,

Carlos L. Pena -S

Carlos L. Peña, PhD, MS
Director
Division of Neurological
and Physical Medicine Devices
Office of Device Evaluation
Center for Devices and Radiological Health



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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Document Control Room - W064-0609
Silver Spring, MD 20993-0002

NovoCure, Ltd.
% Mr. Jonathan S. Kahan
Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, N.W.
Washington, D.C. 20004

APR 8 2011

Re: P100034
NovoTTT-100A System
Filed: August 16, 2010
Amended: September 10, October 19, December 13, and December 27, 2011; and
February 17, and April 8, 2011
Procedure: NZK

Dear Mr. Kahan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the NovoTTT-100A System. This device is indicated for treatment of adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme, following histologically- or radiologically-confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Page 2 - Mr. Jonathan S. Kahan

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

In addition to the conditions outlined above, you must conduct the following post-approval study (PAS):

The New Enrollment Study for NovoTTF-100A in Recurrent GliM Patients: Per agreed on study outline (e-mail dated April 5, 2011) this study will address the following question: Is the overall survival of patients treated with NovoTTF-100A non-inferior to the survival of patients treated with the best standard of care (chemotherapy)? This question will be addressed with a prospective, multi-center, non-randomized, unblinded, concurrent control study of NovoTTF-100A in recurrent Glioblastoma Multiforme (GliM) patients. The study will be conducted in at least 30 sites, at least half of them in the United States, and may include centers with previous experience with the device. Patients 22 years old and older will be included in the PAS. A total of 406 subjects will be enrolled, with 243 subjects per study arm. All study participants will be followed until death. Study follow-up visits include baseline and monthly in-office visits until disease progression. Assessment at baseline includes the Mini Mental State Examination (MMSE) and genetic profiling. The monthly assessments include survival status, MMSE and adverse events assessment. After disease progression study participants will be followed by monthly phone calls to determine survival status.

The primary data analysis will compare overall survival in NovoTTF-100A patients to that seen in concurrent BSC comparison patients, in the investigational device exemption (IDE) study intent-to-treat population, within a predefined confidence interval bound consistent with a performance goal of 1.375. The secondary endpoints will be: Change in neuro-cognitive function from baseline based on the MMSE; Genetic profiling of tumors and correlation with response to NovoTTF-100A treatment, specifically:

- MGMT promoter methylation status
- EGFR amplification, over expression or rearrangement
- Chromosomes 1p/19q deletion status
- Adverse event incidence by body system and term, including:
- Incidence of seizures
- Anticonvulsant use

Page 3 - Mr. Jonathan S. Kahan

Please be advised that the results from these studies should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement.

In addition to the Annual Report requirements, FDA would like to remind you that you are required to submit PAS Progress Reports every six months during the first two years and annually thereafter. The reports should clearly be identified as Post-Approval Study Report. Two copies, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order"

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm>

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA.

Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes a complete protocol of your post-approval study. Your PMA supplement should be clearly labeled as a "Post-Approval Study Protocol" and submitted in triplicate to the address below. Please reference the PMA number above to facilitate processing. If there are multiple protocols being finalized after PMA approval, please submit each protocol as a separate PMA supplement. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm)

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm).

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

3

Page 4 - Mr. Jonathan S. Kahan

device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise become aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or
2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at www.fda.gov/MedicalDevices/Safety/ReportProblem/default.htm.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm.

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at www.fda.gov/MedicalDevices/ProductionandMarketing/Instructions/DeviceApprovalandClearance/PMAApprovals/default.htm. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

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Page 5 - Mr. Jonathan S. Kahan

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing. One of those three copies may be an electronic copy (eCopy), in an electronic format that FDA can process, review and archive (general information:

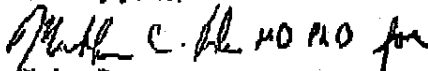
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/howtoattachYourDevice/Pre-marketSubmissions/ucm134508.htm>; clinical and statistical data:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/howtoattachYourDevice/Pre-marketSubmissions/ucm136377.htm>)

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Mail Center - WO66-0609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Ms. Jan C. Callaway at 301-796-5620.

Sincerely yours,



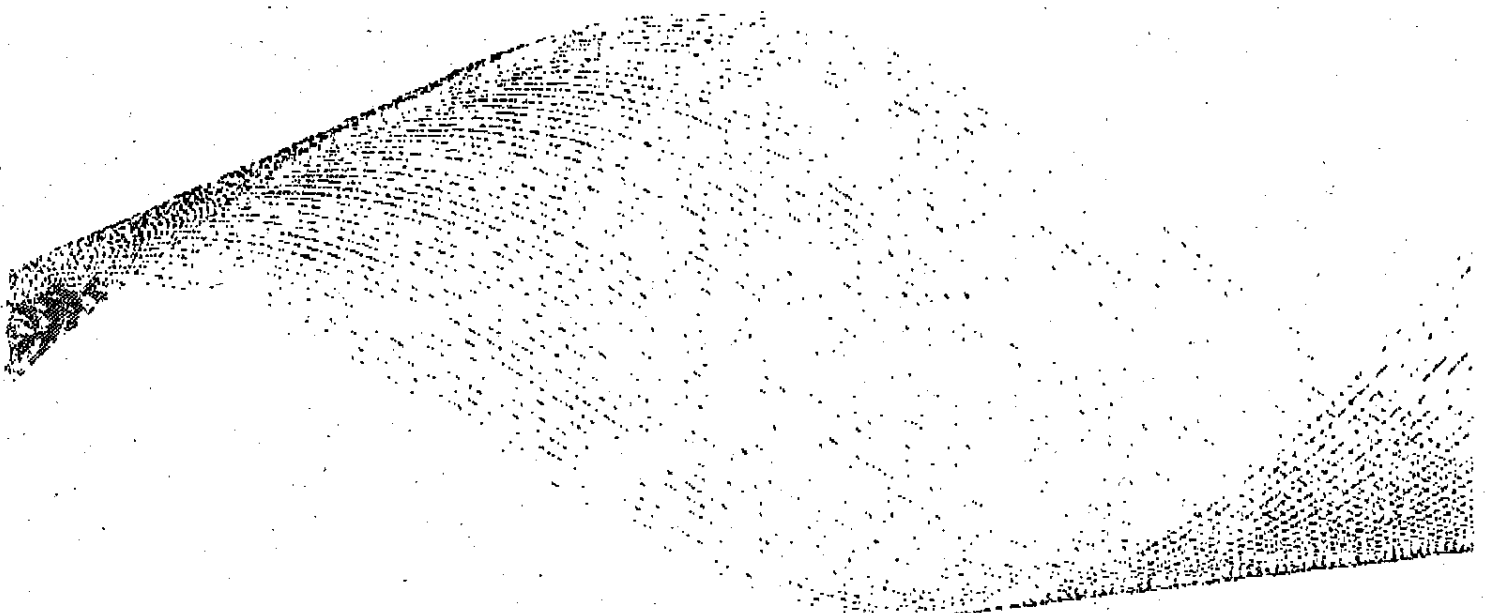
Christy Foreman
Acting Director
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

5

OPTUNE[™]

(NovoTTF[™]-100A System)

INSTRUCTIONS FOR USE



novocure[™]

This manual is intended for physicians prescribing the use of Optune.
Additional information is found in the following materials:
• Patient Information and Operation Manual

Caution: Federal law restricts this device to sale by or on the order of a physician

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Indications for Use

Optune™ is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM).

Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

For the treatment of recurrent GBM, Optune™ is indicated following histologically-or radiologically-confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

Contraindications, Warnings and Precautions

Contraindications

Do not use Optune if you have an active implanted medical device, except device (such as, but not limited to) with no replacement or bulky fragments. Examples of active electronic devices include deep brain stimulators, spinal cord stimulators, vagus nerve stimulators, pacemakers, defibrillators, and programmable shunts. Use of Optune together with implanted electronic devices has not been tested and may theoretically lead to malfunctioning of the implanted device. Use of Optune together with skull defects or bullet fragments has not been tested and may possibly lead to tissue damage or render Optune ineffective.

Do not use Optune if you are known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the gel used with Optune may occasionally cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings

Warning - Use Optune only after receiving training from qualified personnel, such as your doctor, nurse, or other medical personnel who have completed a training course given by the device manufacturer (Novocure). Ask to see a certificate signed by Novocure that says they completed a training course. Your training will include a detailed review of this manual and practice in the use of the system. In addition, you will be trained in what to do if there are problems with treatment. Use of Optune without receiving this training can result in breaks in treatment and may rarely cause increased scalp rash, open sores on your head, allergic reactions or even an electric shock.

Warning - Optune is not intended to be used as a substitute for chemotherapy but rather as an adjunct to treatment with TMZ for newly diagnosed GBM.

Warning - Do not use Optune if you are 21 years old or younger. It is unknown what side effects the device may cause in these cases or if it will be effective.

Warning - Do not use Optune if you are pregnant, you think you might be pregnant, or are trying to get pregnant. If you are a woman who is able to get pregnant, you must use birth control when using the device. Optune was not tested in pregnant women. It is unknown what side effects the device may cause if you are pregnant or if it will be effective.

Warning - In case of skin irritation, which appears as redness under the transducer arrays (a mild rash), use high-potency topical steroid (hydrocortisone cream) when replacing transducer arrays. This will help relieve your skin irritation. If you do not use this cream, the skin irritation can become more serious and may even lead to skin break down, infections, pain and blisters. If this happens, stop using the topical steroid cream and contact your doctor. Your doctor will supply you with an antibiotic cream to use when replacing transducer arrays. If you do not use this cream, your symptoms may continue and your doctor may ask you to take a break from treatment until your skin heals. Taking a break from treatment may lower your chance to respond to treatment.

Warning - All servicing procedures must be performed by qualified and trained personnel. If you attempt to open and service the system alone you may cause damage to the system. You could also get an electric shock by touching the inner parts of the device.

Precautions

Caution - Keep Optune out of the reach of children. If children touch the device, they could damage the device. This could cause a break in treatment. Breaks in treatment may lower your chance to respond to treatment.

Caution - Do not use any parts that do not come with the Optune Treatment Kit, or that were not sent to you by the device manufacturer or given to you by your doctor. Use of other parts, manufactured by other companies or for use with other devices, can damage the device. This may lead to a break in treatment. Breaks in treatment may lower your chance to respond to treatment.

Caution - If your doctor used plates or screws to close your skull bone during your surgery, be careful when placing the transducer arrays. Make sure the round disks that make up the transducer arrays are not on top of the areas where you can feel the screws or plates under your skin. In other words, make sure the screws or plates under your skin are in between the round disks that make up the transducer arrays. If you do not do this, you may have increased skin damage which may lead to a break in treatment. Breaks in treatment may lower the chance of the device being effective.

Caution - Tell your doctor before using the device if you have an inactive implanted medical device in the brain (for example, stents, plastic drug delivery reservoir, aneurysm clips or coils, device leads). Use of Optune in subjects with inactive implanted medical devices in their brain was not been tested and could lead to tissue damage or lower the chance of the device being effective.

Caution - Do not use Optune if any parts look damaged (loose wires, loose connectors, loose sockets, cracks or breaks in the plastic case). Use of damaged components can damage the device, and cause a break in treatment. Breaks in treatment may lower your chance to respond to treatment.

Caution - Do not wet the device or transducer arrays. Getting the device wet may damage it, preventing you from receiving treatment for the right amount of time. Getting the transducer arrays very wet is likely to cause the transducer arrays to come loose from your head. If this happens, the device will turn off and you will need to change the transducer arrays.

Caution - Before connecting or disconnecting the transducer arrays, make sure that the Optune power switch is in the Off position. Disconnecting transducer arrays with the device power switch in the On position may cause a device alarm to go off, and could damage the device.

Caution - If you have an underlying serious skin condition on the scalp, discuss with your doctor whether this may prevent or temporarily interfere with Optune treatment.

Notices

Notice! The Optune device and transducer arrays will activate metal detectors.

Notice! Do not use Optune if your tumor is located in the lower parts of the brain close to the spinal cord. Ask your doctor if your tumor is located in this part of your brain. Optune has not been tested in patients with tumors in these locations. It is unknown whether these tumors will respond to treatment.

Notice! You should use Optune for at least 18 hours a day to get the best response to treatment. Using Optune for less than 18 hours a day lowers the chances that you will respond to treatment.

Notice! Do not stop using Optune before you finish at least four full weeks of therapy to get the best response to treatment. Stopping treatment before four weeks lowers the chances that you will respond to treatment.

Notice! Do not stop using Optune even if you have used it less than the recommended 18 hours per day. You should stop using the device only if your doctor tells you to. Stopping treatment could lower the chances that you will respond to treatment.

Notice! If you plan to be away from home for more than 2 hours, carry an extra battery and/or the power supply with you in case the battery you are using runs out. If you do not take a spare battery and/or the power supply you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! Make sure you have at least 12 extra transducer arrays at all times. This will last you until the next transducer array shipment arrives. Remember to order more transducer arrays when there are at least 12 extra transducer arrays left. If you do not order transducer arrays in time you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! Batteries may weaken over time and need to be replaced. You will know this has happened when the amount of time the device can run on a fully charged battery begins to shorten. For example, if the low battery indicator light flashes within only 1.5 hours from the start of treatment, replace the battery. If you do not have replacement batteries when your batteries run out, you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! You should carry the Troubleshooting Guide (Section 26) at all times. This guide is necessary to ensure Optune works properly. If you do not work the system correctly you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! Do not block the device vents located on the sides of the Optune device. Blocking the vents may cause the device to overheat and turn off, leading to a break in treatment. If this happens, unblock the vents, wait 5 minutes and restart the device.

Notice! Do not block the battery charger vents located on the front of the battery chargers. Blocking the vents may cause the charger to overheat. This could prevent your batteries from charging.

Notice! Before using a transducer array, make sure its package is sealed by gently rubbing the package between thumb and pointer finger on all four sides. The package should be closed on all sides. There should be no openings in the package seal. If the package is not sealed, the transducer array may be damaged. A damaged transducer array will not work properly and may cause the device to turn off.

Notice! The transducer arrays are for single use and should not be taken off your head and put back on again. If you put a used transducer array back on your head again, it may not stick well to your skin and the device could turn off.

Description

Optune, for the treatment of newly diagnosed and/or recurrent GBM, is a portable battery or power supply operated device which produces alternating electrical fields, called tumor treatment fields (TTFields) within the human body. TTFields are applied to the patient by electrically-insulated surface transducer arrays. TTFields disrupt the rapid cell division exhibited by cancer cells.

Optune is comprised of two main components: (1) an Electric Field Generator (the Optune device); and (2) INE Insulated Transducer Arrays (the transducer arrays). In addition, the following components are also included in the Optune Treatment Kit: power supply, portable battery, battery rack, battery charger, connection cable and carrying case.

Treatment parameters are preset by Novocure such that there are no electrical output adjustments available to the patient. The patient must learn to change and recharge depleted device batteries and to connect to an external power supply overnight. In addition, the transducer arrays need to be replaced once to twice a week and the scalp re-shaved in order to maintain optimal contact. Patients carry the device in an over-the-shoulder bag or backpack and receive continuous treatment without changing their daily routine.

1 Kirson, E. D., V. Obeid et al. (2007). "Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors." *Proc. Natl. Acad. Sci. USA* 104(24): 10152-7

Principles of Operation

Optune produces alternating electrical fields within the human body that disrupt the rapid cell division exhibited by cancer cells, with the alternating electrical fields applied to the brain through transducer arrays placed on the scalp.

TTFields harness electric fields to arrest the proliferation of tumor cells and to destroy them. The TTField technology takes advantage of the special characteristics and geometrical shape of dividing cells, which make them susceptible to the effects of the alternating electric TTFields. These special fields alter the tumor cell polarity at an intermediate frequency (on the order of 100-300 kHz). The frequency used for a particular treatment is specific to the cell type being treated (e.g., 200kHz for GBM).

In contrast, the TTFields have not been shown to have an effect on cells that are not undergoing division. Since most normal adult brain cells proliferate very slowly, if at all, they are hypothesized to be little affected by the TTFields. Testing demonstrates no differences between treated and control animals in histology of the major internal organs (including the brain), blood examination, cardiac rhythm, body temperature, or in animal behavior. In addition, because the fields alternate so rapidly, they have no effect on normal quiescent cells nor do they stimulate nerves and muscles. It is noted that, because TTFields are only applied to the brain, they have no effect on rapidly proliferating cells in the rest of the body. The intensities of the electric fields within the tissues are very small and do not result in any meaningful increase in tissue temperature. Thus, TTField application has the advantage of being highly selective and is not expected to be associated with significant toxicity.

The above mechanisms of action are consistent with the extensive research regarding the effects of TTFields. These results demonstrate both disruption of cell division up to complete cessation of the process, as well as complete destruction of the dividing cells. It is important to note that all the described effects can be obtained by fields of low intensity such that they are not accompanied by any significant elevation of temperature.

Preclinical Data

TTFields have been shown both in vitro and in vivo to effectively inhibit cancer cell replication during mitosis without any systemic side effects. At intensities of approximately 1 V/cm, TTFields can be frequency-tuned to effectively inhibit different cancer cell types (i.e., the smaller the cell, the higher the frequency needed). Due to disruption of microtubule polymerization and physical disruption of cell integrity at the cleavage plane during telophase²

Specifically, TTFields have been shown to inhibit glioblastoma cells in vitro and in vivo at a frequency of 200 kHz and an intensity of 0.7 V/cm. Based on realistic finite element mesh simulations and direct measurements of TTFields intensity in experimental animals and in the human brain, Novocure has concluded that effective TTField intensities can be generated in the brains of large animals and humans. Extensive safety studies in healthy animals (mice, rats and rabbits) have shown that TTFields are not associated with significant systemic toxicities. Neither acute, nor chronic systemic toxicities were seen when TTFields were applied to the torso or head, at different frequencies (100-200 kHz), different intensities and for different periods of time.³

Using a model developed to simulate the growth kinetics of a malignant tumor, the minimal treatment course duration for Optune has been determined to be approximately 4 weeks to reach tumor stabilization. Stopping treatment prior to completion of a 4 week treatment course will most likely lead to continued tumor growth and appearance of symptoms within approximately 1-2 weeks.

2 Kirson, E.D., & Gurvich, et al. (2004). "Disruption of cancer cell replication by alternating electric fields." *Cancer Res.* 64(9): 3288-95.

3 Kirson, E.D., V. Dabaly, et al. (2007).

Clinical Data

NEWLY DIAGNOSED GLIOBLASTOMA (see page 17 for recurrent GBM)

Pilot Clinical Study in Newly Diagnosed GBM

Optune together with temozolomide (TMZ) has been tested in ten newly diagnosed GBM subjects in a single center, pilot study in Europe. Median progression free survival (PFS) of the patients in this study exceeded historical controls (14.4 months versus 7.1 months, respectively). At the end of the study (4 years from initiation) 5 of the 10 patients died; of the remaining 5 patients 2 were lost to follow up and 3 were reported alive and progression free. Median OS from diagnosis was greater than 40 months (compared to 14.7 months in historical controls). The only device related adverse event (AE) seen in this trial was a mild to moderate skin irritation beneath the device transducer arrays.

Pivotal Clinical Study in Newly Diagnosed GBM

Study Design: The study was a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of newly diagnosed GBM subjects treated with Optune and Temozolomide (TMZ) to those treated with TMZ alone.

The following were the objectives of the study:

To prospectively compare the progression free survival and overall survival of newly diagnosed GBM subjects treated with Optune and TMZ to those treated TMZ alone.

To collect evidence of the safety of TFields applied to subjects with newly diagnosed GBM using Optune.

Eligibility Criteria: The inclusion and exclusion criteria for the trial were as follows:

Inclusion Criteria

- Pathological evidence of GBM using WHO classification criteria
- ≥ 18 years of age.
- Received maximal debulking surgery and radiotherapy concomitant with Temozolomide (45-70Gy):
 - Patients may enroll in the study if received Gliadel wafers before entering the trial
 - Any additional treatments received prior to enrollment will be considered an exclusion
 - Minimal dose for concomitant radiotherapy is 45 Gy
- Karnofsky scale ≥ 70
- Life expectancy at least 3 months
- Participants of childbearing age must use effective contraception
- All patients must sign written informed consent
- Treatment start date at least 4 weeks out from surgery.
- Treatment start date at least 4 weeks out but not more than 7 weeks from the later of last dose of concomitant temozolomide or radiotherapy

Exclusion Criteria

- Progressive disease (according to MacDonald Criteria). If pseudoprogression is suspected, additional imaging studies must be performed to rule out true progression.
- Actively participating in another clinical treatment trial
- Pregnant
- Significant co-morbidities at baseline which would prevent maintenance Temozolomide treatment:
 - Thrombocytopenia (platelet count $< 100 \times 10^3/\mu\text{L}$)
 - Neutropenia (absolute neutrophil count $< 15 \times 10^3/\mu\text{L}$)
 - CTC grade 4 non-hematological Toxicity (except for alopecia, nausea, vomiting)
 - Significant liver function impairment - AST or ALT > 3 times the upper limit of normal
 - Total bilirubin $>$ upper limit of normal
 - Significant renal impairment (serum creatinine $> 1.7 \text{ mg/dL}$)
- Implanted pacemaker, programmable shunts, defibrillator, deep brain stimulator, other implanted electronic devices in the brain, or documented clinically significant arrhythmias.
- Intra-tentorial tumor
- Evidence of increased intracranial pressure (midline shift $> 5\text{mm}$, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)
- History of hypersensitivity reaction to Temozolomide or a history of hypersensitivity to DHC.

Study Procedures:

Treatment Arm

Optune was given together with maintenance TMZ. At treatment initiation patients were seen at an outpatient clinic. During this visit baseline examinations were performed and Optune treatment initiated. The patients were instructed on the operation of Optune and battery replacement. Once the patients were trained in operating the device they were released to continue treatment at home. The patients received multiple 1 month courses of continuous Optune treatment. Patients were treated with maintenance TMZ according to the standard dosing regimen. Following radiological progression or unacceptable toxicity, TMZ could be replaced with best standard of care second line therapy.

Control Arm

All subjects had baseline examinations performed prior to treatment initiation. Patients were treated with maintenance TMZ according to the standard dosing regimen. Following radiological progression or unacceptable toxicity, TMZ could be replaced with best standard of care second line therapy.

Follow-up

During treatment all patients were seen once every month at an outpatient clinic where they underwent medical follow-up and routine laboratory exams. An MRI was performed every second month following the baseline MRI until second progression or 24 months (whichever came first, when treatment on both arms of the study was terminated). In the case of clinical progression an unscheduled MRI was obtained within 1 week of the investigator becoming aware of the clinical progression. No additional MRIs were required after second progression. Central MRI review was performed by a neuro-radiologist blinded to the treatment group of each patient. Medical follow-up continued for 2 months after treatment termination in order to capture treatment related toxicities. After these visits, mortality was assessed based on monthly telephone interviews with the patients or the patients' caregivers.

Analyses: Two analyses were performed in the study: An interim analysis on the first 315 patients with a minimum of 18 months follow-up and a final analysis on the full study cohort of 695 patients.

Protocol Deviations: Major protocol deviations were defined as deviations that have the potential to influence the primary and secondary efficacy endpoints of the study. There were a total of 13 major protocol deviations in the interim analysis and a total of 24 major protocol violations at the final analysis.

In the interim analysis dataset, 2 patients received experimental chemotherapies as part of other clinical trials together with their standard of care temozolomide (1 in each treatment arm). In addition, 11 patients in the TMZ alone arm received Optune treatment through prescription at other institutions. This deviation was termed "crossover" although no official crossover was allowed in the protocol, and Optune therapy was given without sponsor or investigator consent.

In the final analysis dataset, 2 patients received experimental chemotherapies as part of other clinical trials together with their standard of care temozolomide (1 in each treatment arm). In addition, 22 patients in the TMZ alone arm received Optune treatment through prescription at other institutions. This deviation was termed "crossover" although no official crossover was allowed in the protocol, and Optune therapy was given without sponsor or investigator consent.

Analysis Populations: Progression free survival was analyzed in the intent to treat (ITT) population which included all randomized subjects: 10 Optune / TMZ and 105 TMZ alone at the interim analysis; 466 Optune / TMZ and 229 TMZ alone at the final analysis). Overall survival was analyzed in the per protocol (PP) population which included all patients receiving at least the first course of TMZ and had no major protocol deviations (196 Optune / TMZ and 84 TMZ alone at the interim analysis; 429 Optune / TMZ and 180 TMZ alone at the final analysis). Major protocol deviations included patients who received other experimental therapies on protocol or crossed over from the TMZ alone arm to Optune / TMZ.

Subject Characteristics: 315 subjects (210 Optune/TMZ; 105 TMZ) with newly diagnosed GBM were enrolled in the interim analysis of the study. Baseline characteristics in the ITT population were as follows:

| Baseline Characteristic | Treatment Group | |
|-------------------------------------------------|-----------------|-----------------|
| | Optune/TMZ | TMZ Alone |
| | (N=210) n(%) | (N=105) n(%) |
| Gender | | |
| Male | 140 (66.67) | 67 (63.81) |
| Female | 70 (33.33) | 38 (36.19) |
| Central MGMT Assessment | | |
| Invalid | 24 (11.43) | 11 (10.48) |
| Unknown | 58 (27.62) | 30 (28.57) |
| Methylated | 49 (23.33) | 26 (24.76) |
| Unmethylated | 79 (37.62) | 38 (36.19) |
| Extent of Resection | | |
| Biopsy | 23 (10.95) | 11 (10.48) |
| Gross Total Resection | 135 (64.29) | 67 (63.81) |
| Partial Resection | 52 (24.76) | 27 (25.71) |
| Area | | |
| ROW | 83 (39.52) | 41 (39.05) |
| USA | 127 (60.48) | 64 (60.95) |
| Tumor Position | | |
| Missing | 0 (0) | 3 (2.86) |
| Corpus Callosum | 12 (5.71) | 3 (2.86) |
| Frontal Lobe | 64 (30.48) | 32 (30.48) |
| Occipital Lobe | 7 (3.33) | 4 (3.81) |
| Parietal Lobe | 35 (16.67) | 27 (25.71) |
| Temporal Lobe | 92 (43.81) | 36 (34.29) |
| Tumor Location | | |
| Missing | 0 (0) | 1 (0.95) |
| Both | 2 (0.95) | 1 (0.95) |
| Corpus Callosum | 8 (3.81) | 3 (2.86) |
| Left | 93 (44.29) | 41 (39.05) |
| Right | 107 (50.95) | 59 (56.19) |
| Karnofsky Performance Score | Median | 90 |
| | Min, Max | 60, 100 |
| Age In Years | Median | 57 |
| | Min, Max | 20, 83 |
| No. of Cycles of TMZ Received | Median | 6 |
| | Min, Max | 1, 26 |
| No. of Cycles of Optune Received | Median | 9 |
| | Min, Max | 1, 58 |
| Time from GBM Diagnosis to Randomization (Days) | Median | 115 |
| | Min, Max | 59, 171 |

As seen above, all baseline characteristics are well balanced between arms in the ITT population at the interim analysis. The baseline characteristics of the PP population also remained well balanced between treatment arms. As noted in the table above, 35 patients (11.11%) had tissue that was not evaluable, and 88 patients (27.94%) did not have tissue available for analysis.

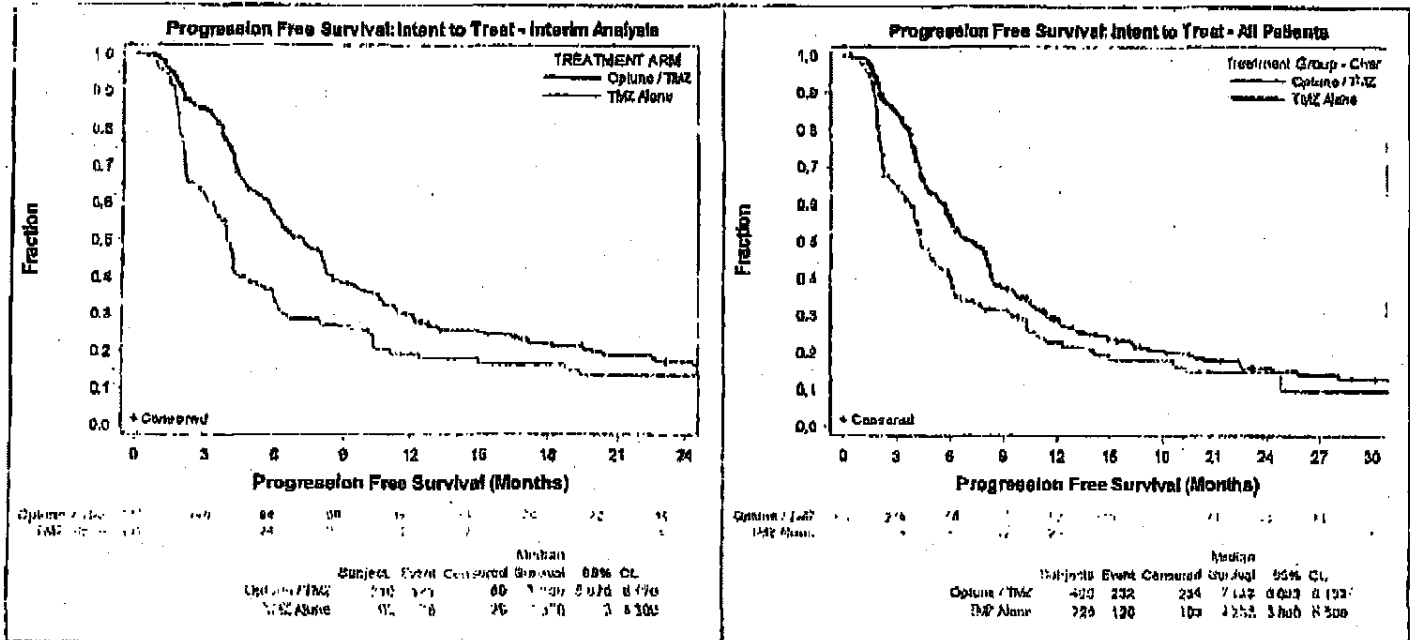
695 subjects (466 Optune / TMZ; 229 TMZ alone) with newly diagnosed GBM were enrolled in the study and had CRF information available at the time of the final analysis. Baseline characteristics in the ITT population were as follows:

| Baseline Characteristic | | Treatment Group | |
|-------------------------------------------------|----------|-------------------------------|------------------------------|
| | | Optune/TMZ (N=466) n(%) | TMZ Alone (N=229) n(%) |
| Gender | | | |
| Male | | 316 (67.8) | 157 (68.56) |
| Female | | 150 (32.19) | 72 (31.44) |
| Central MGMT Assessment | | | |
| Invalid | | 46 (9.87) | 18 (7.86) |
| Unknown | | 106 (22.75) | 57 (24.89) |
| Methylated | | 127 (27.25) | 67 (29.26) |
| Unmethylated | | 107 (40.13) | 87 (37.99) |
| Extent of Resection | | | |
| Biopsy | | 61 (13.09) | 30 (13.1) |
| Gross Total Resection | | 253 (54.29) | 124 (54.15) |
| Partial Resection | | 152 (32.62) | 75 (32.75) |
| Area | | | |
| ROW | | 245 (52.58) | 111 (48.47) |
| USA | | 221 (47.42) | 118 (51.53) |
| Tumor Position | | | |
| Missing | | 31 (6.65) | 15 (6.55) |
| Corpus Callosum | | 21 (4.51) | 9 (3.93) |
| Frontal Lobe | | 142 (30.47) | 67 (29.26) |
| Occipital Lobe | | 14 (3) | 4 (1.75) |
| Parietal Lobe | | 77 (16.52) | 50 (21.83) |
| Temporal Lobe | | 181 (38.84) | 84 (36.68) |
| Tumor Location | | | |
| Missing | | 30 (6.44) | 12 (5.24) |
| Both | | 12 (2.58) | 3 (1.31) |
| Corpus Callosum | | 12 (2.58) | 7 (3.06) |
| Left | | 193 (41.42) | 93 (40.61) |
| Right | | 219 (47) | 114 (49.78) |
| Karnofsky Performance Score | Median | 90 | 90 |
| | Min, Max | 60, 100 | 70, 100 |
| Age in Years | Median | 56 | 57 |
| | Min, Max | 19, 85 | 19, 83 |
| No. of Cycles of TMZ Received | Median | | 4 |
| | Min, Max | 1, 26 | 1, 24 |
| No. of Cycles of Optune Received | Median | 6 | 0 |
| | Min, Max | 1, 58 | 0, 0 |
| Time from GBM Diagnosis to Randomization (Days) | Median | 113 | 111 |
| | Min, Max | 59, 496 | 43, 500 |

As seen above, all baseline characteristics are well balanced between arms in the ITT population at the final analysis. The baseline characteristics of the PP population also remained well balanced between treatment arms. As noted in the table above, 64 patients (9.21%) had tissue that was not evaluable, and 163 patients (23.45%) did not have tissue available for analysis.

Effectiveness Results:**Primary Effectiveness Endpoint: Progression Free Survival at the Interim Analysis**

The threshold for statistical significance based on the Lan-DeMets O'Brien-Fleming method at the interim analysis was pre defined as $p=0.01394$, and the test was to be performed in the ITT population according to the protocol. In the ITT population, which included all-randomized subjects (Optune/TMZ=210, TMZ alone=105), PFS at the interim analysis met this threshold. The difference of more than 3 months in median PFS is highly clinically significant. The Hazard Ratio for PFS was 0.621, which translates into a 37.9% decrease in the risk of progression when using Optune/TMZ compared to TMZ alone. At the final analysis, which included 695 patients (Optune/TMZ=466, TMZ alone=229), PFS was also highly significant with a hazard ratio of 0.694.

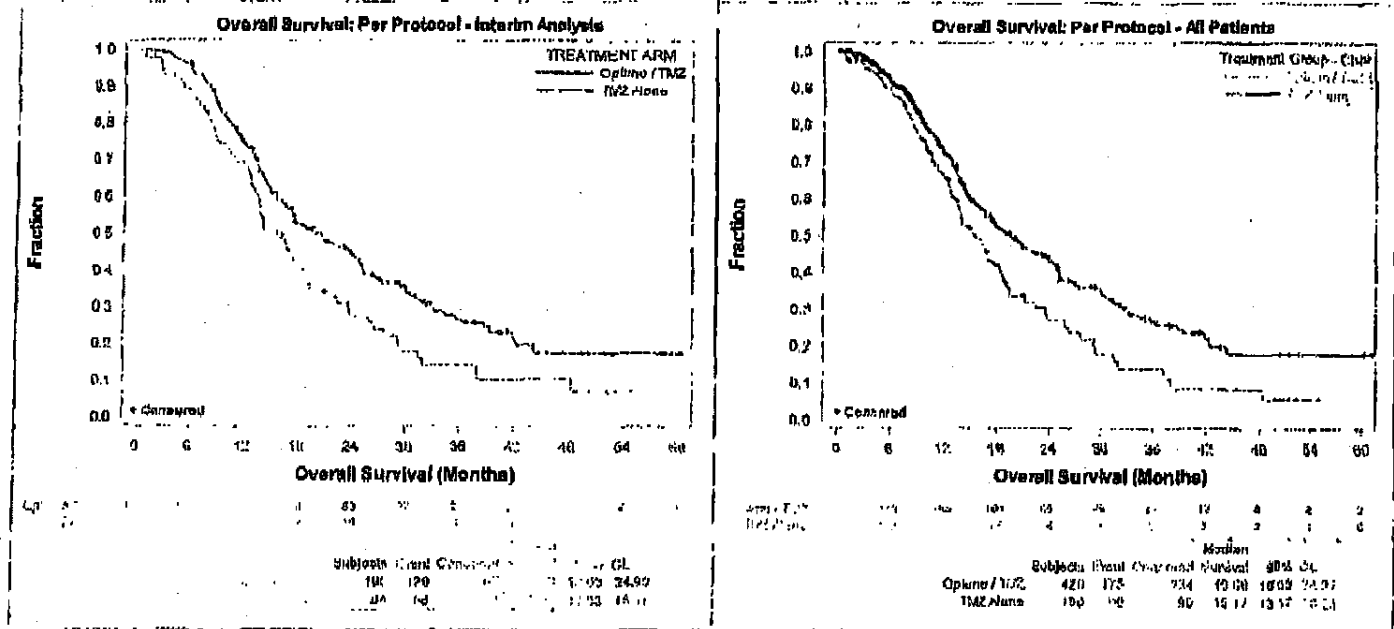
Primary Efficacy Endpoint - Progression Free Survival (ITT)

| | Interim Analysis | | Final Analysis | |
|-----------------------|----------------------|----------------|----------------------|----------------|
| | Optune/TMZ | TMZ Alone | Optune/TMZ | TMZ Alone |
| Median (95% CI) | 7.2 (5.9, 8.2) | 4.0 (3.0, 4.3) | 7.1 (6.0, 8.1) | 4.2 (3.9, 5.5) |
| Log-rank test | $p=0.0015$ | | $p=0.0010$ | |
| Hazard Ratio (95% CI) | 0.621 (0.468, 0.823) | | 0.694 (0.558, 0.823) | |

Although not a pre-specified endpoint, PFS was also analyzed in the PP population at the interim and final analyses. Median PFS in the PP population was identical to the ITT population at the interim analysis and slightly longer than the ITT population at the final analysis. Notably, median PFS remained significantly higher in the Optune/TMZ group than in the TMZ alone group in the PP population at both the interim and final analyses.

Powered Secondary Effectiveness Endpoint: Overall Survival at the Interim Analysis

Overall survival (OS) was a secondary endpoint in the trial. The threshold for superior OS at the interim analysis was predefined in the protocol and was to be tested in the PP population. In the PP population, which was analyzed at the interim analysis, the treatment arms actually received (as treated) Optune/TMZ (N=196, TMZ alone (N=180). OS was also significantly longer in the Optune/TMZ group compared to the TMZ alone group. An increase of almost 3 months as seen here is highly significant clinically, statistically (log-rank $p=0.0042$). This translates into a 54% decrease in the risk of death when using Optune/TMZ compared to TMZ alone. At the final analysis, which included 693 patients (Optune/TMZ=420, TMZ alone=180), OS was also highly significant with a hazard ratio of 0.685.

Overall Survival (PP)

| | Interim Analysis | | Final Analysis | |
|-----------------------|----------------------|-------------------|----------------------|-------------------|
| | Optune/TMZ | TMZ Alone | Optune/TMZ | TMZ Alone |
| Median (95% CI) | 20.5 (16.6, 24.9) | 15.6 (12.9, 18.5) | 19.6 (16.6, 24.1) | 15.2 (13.5, 18.2) |
| Log-rank test | p=0.0042 | | p=0.0030 | |
| Hazard Ratio (95% CI) | 0.666 (0.495, 0.898) | | 0.685 (0.529, 0.882) | |

Although not a pre-specified secondary endpoint, OS was also analyzed in the ITT population. At the interim analysis, OS in the ITT population was also significantly longer in the Optune/TMZ arm compared to TMZ alone by almost 20%. The median OS was 19.6 months (95% CI 16.6-24.1) in the Optune/TMZ group and 15.6 months in the TMZ alone group (95% CI 12.9-18.5). An increase of 3 months as seen here is highly significant both statistically (log-rank $p=0.0338$) and clinically. The hazard ratio for OS was 0.744 using a Cox regression analysis. This translates into a 24% decrease in the risk of death when using Optune/TMZ compared to TMZ alone.

Furthermore, at the final analysis, OS in the ITT population was also significantly longer in the Optune/TMZ arm compared to TMZ alone by 17%. The median OS was 19.6 months (95% CI 16.6-24.1) in the Optune/TMZ group and 15.5 months in the TMZ alone group (95% CI 13.7-18.5). An increase of almost 3 months as seen here is highly significant statistically and clinically (log-rank $p=0.0229$). The hazard ratio for OS was 0.754 using a Cox regression analysis. This translates into a 24% decrease in the risk of death when using Optune/TMZ compared to TMZ alone.

Secondary Endpoints: Secondary endpoints also showed an advantage for Optune/TMZ compared to TMZ alone. The results below are from the interim analysis which included 315 patients (210 Optune/TMZ and 105 TMZ alone):

| Endpoint | Optune/TMZ | TMZ Alone | P-Value |
|---------------------------------------------|------------|-----------|---------|
| Progression Free Survival at 6 months (ITT) | 56.7% | 33.7% | 0.0004 |
| 1-year survival (PP) | 75% | 69% | 0.151 |
| 2-year survival (PP) | 48% | 32% | 0.0056 |
| Complete response rate (ITT) | 9% | 3.5% | NA |

In addition, although not a pre-specified endpoint, 1- and 2-year survival were also analyzed in the ITT population at the interim analysis. In the ITT population, 1-year survival was 75% in the Optune/TMZ group and 70% in the TMZ alone group (p-value=0.162) at the interim analysis. 2-year survival in the ITT population at the interim analysis was 48% in the Optune/TMZ group and 34% in the TMZ alone group (p-value=0.0122). Furthermore, the 1-year survival rates at the final analysis are shown in the table below:

| Endpoint | Optune/TMZ | TMZ Alone | P-Value |
|-----------------------|------------|-----------|---------|
| 1-year survival (PP) | 69% | 63% | 0.131 |
| 1-year survival (ITT) | 69% | 66% | 0.265 |

Quality of Life: Quality of Life assessments were based on the interim analysis cohort of 315 subjects. Quality of life, cognitive function and functional status were all maintained throughout treatment with the device, leading to the clear conclusion that use of Optune does not harm patients' quality of life, cognitive function or ability to perform activities of daily living.

Safety Results: Safety was assessed on all patients at the final analysis who received the treatment at the time of the analysis (Optune/TMZ: 437, TMZ alone: 207). A slightly higher incidence of grade 1-2 adverse events was seen in some of the systems in the Optune/TMZ arm of the study. This is most likely a reflection of the longer duration on TMZ treatment in these patients (median of 6 cycles versus 4 cycles in the control arm) due to the increase in PFS seen in the treatment group. Grade 3+ adverse events were well balanced between arms. None of the grade 3-5 adverse events in these body systems were considered related to Optune by any of the investigators except for 1% grade 3 skin irritation.

All Adverse Events by Body System and Severity (Safety Population)

| System Organ Class | Optune/TMZ (N=437) | | | TMZ Alone (N=207) | | |
|----------------------------------------------------------------------|-----------------------|-----------|---------|----------------------|----------|---------|
| | Low-Medium | Severe | Fatal | Low-Medium | Severe | Fatal |
| Number of Patients with ≥1 AE | 211 (49%) | 169 (39%) | 35 (8%) | 91 (44%) | 82 (40%) | 7 (3%) |
| Blood and Lymphatic System Disorders | 66 (20%) | 7 (1%) | 0 | 49 (24%) | 21 (10%) | 0 |
| Cardiac Disorders | 17 (3%) | 1 (0%) | 3 (1%) | 6 (3%) | 4 (2%) | 0 |
| Ear and Labyrinth Disorders | 25 (6%) | 0 | 0 | 8 (4%) | 0 | 0 |
| Endocrine Disorders | 11 (3%) | 0 | 0 | 4 (2%) | 0 | 0 |
| Eye Disorders | 76 (9%) | 5 (1%) | 1 | 15 (7%) | 2 (1%) | 0 |
| Gastrointestinal Disorders | 202 (46%) | 18 (4%) | 0 | 76 (37%) | 4 (2%) | 0 |
| General Disorders and Administration Site Conditions | 175 (40%) | 27 (6%) | 1 (<1%) | 76 (37%) | 10 (5%) | 1 (<1%) |
| Hepatobiliary Disorders | 1 (<1%) | 1 (<1%) | 0 | 3 (2%) | 0 | 0 |
| Liver Disorder | 1 (<1%) | 0 | 0 | 3 (2%) | 0 | 0 |
| Immune System Disorders | 10 (2%) | 0 | 0 | 7 (3%) | 0 | 0 |
| Infections and Infestations | 17 (2%) | 19 (4%) | 3 (1%) | 56 (27%) | 6 (3%) | 1 (<1%) |
| Injury, Poisoning and Procedural Complications | 216 (49%) | 20 (5%) | 0 | 13 (6%) | 4 (2%) | 0 |
| Abnormal Laboratory Tests | 58 (13%) | 19 (4%) | 0 | 19 (10%) | 7 (3%) | 1 (<1%) |
| Metabolism and Nutrition Disorders | 69 (25%) | 12 (3%) | 0 | 44 (21%) | 6 (3%) | 0 |
| Musculoskeletal and Connective Tissue Disorders | 38 (12%) | 16 (4%) | 0 | 44 (21%) | 8 (4%) | 0 |
| Neoplasms Benign, Malignant and Unspecified (incl. Cysts and Polyps) | 5 (1%) | 1 (<1%) | 2 (<1%) | 2 (1%) | 1 (<1%) | 1 (<1%) |
| Nervous System Disorder | 150 (33%) | 83 (19%) | 3 (1%) | 75 (36%) | 42 (20%) | 0 |
| - Trembling Disorders | 108 (25%) | 36 (8%) | 0 | 38 (18%) | 6 (3%) | 0 |
| - Renal and Urinary Disorders | 42 (10%) | 0 | 0 | 8 (4%) | 1 (1%) | 0 |
| Reproductive System and Breast Disorders | 4 (2%) | 0 | 0 | 3 (1%) | 0 | 0 |
| Skin and Subcutaneous Tissue Disorders | 104 (24%) | 0 | 0 | 32 (15%) | 1 (<1%) | 0 |
| Surgical and Medical Procedures | 2 (<1%) | 0 | 0 | 1 (1%) | 0 | 0 |
| Vascular Disorders | 48 (11%) | 16 (4%) | 1 (<1%) | 19 (9%) | 10 (5%) | 3 (1%) |

Patients treated with Optune/TMZ experienced a small increase in TMZ related AEs and SAEs due to the longer TMZ exposure afforded to these patients by their longer PFS. The only AEs which may have been caused by Optune therapy are the known skin irritation seen in 45% of patients in this study (1% severe), falls which were seen at a slightly higher incidence in patients carrying the device, headaches related to wearing the arrays 24 hours a day and mild psychiatric symptoms (anxiety, insomnia, confusion) which could be caused by the need to incorporate the device and arrays into daily life. No SAEs were considered related to device use. The remainder of AEs and SAEs seen in the trial were well balanced between treatment arms. In conclusion, Optune is very well tolerated with mild to moderate toxicity mostly related to array contact with the scalp.

Conclusions: Optune is a portable, battery operated device which delivers 13 fields to patients with recurrent diagnosed GBM. The results of the pivotal trial in newly diagnosed GBM showed that Optune/TMZ extends progression free and overall survival significantly compared to patients receiving TMZ alone. No significant increase in adverse events is seen when Optune treatment is added to TMZ. The only common device-related AE was a skin irritation seen beneath the transducer arrays in 45% percent of patients. The majority (44 of 45%) of these events were mild to moderate. Based on an assessment of the Quality of life of the interim analysis cohort of 315 patients, cognitive function and functional status did not decline due to the use of Optune/TMZ.

RECURRENT DIAGNOSED GLIOBLASTOMA

Pilot Clinical Study in Recurrent GBM

Optune has been tested in 10 recurrent GBM subjects in a single center, pilot study in Europe. In this study, Optune monotherapy led to a significant increase in time to progression (from 13 to 26 weeks; $p=0.013$), progression free survival at 6 months (PFS6) (from 15 to 50%) and overall survival (OS) (from 6.0 to 14.7 months; $p=0.002$) compared to matched chromosomal and historical comparator groups. The only device related adverse event (AE) seen in this trial was a mild to moderate skin irritation beneath the device transducer arrays.

Other Clinical Experience in Recurrent GBM

The Patient Registry Dataset (PRiDe) is a post-marketing registry of all recurrent GBM patients who received Optune in a real world clinical practice setting in the US between 2011 and 2015. The registry included 457 recurrent GBM patients who received Optune in 91 US cancer centers. More patients in PRiDe than the pivotal clinical trial in recurrent GBM (EF-11) received Optune for first recurrence (33% vs. 9%) and had received prior bevacizumab therapy (55.1% vs. 39%). Median OS was significantly longer with Optune in clinical practice (PRiDe data set) than in the EF-11 pivotal trial in recurrent GBM (9.6 vs. 6.6 months). One- and 2-year OS rates were more than double for NovoTIF Therapy patients in PRiDe than in the EF-11 trial (1-year: 44% vs. 20%; 2-year: 30% vs. 9%). Favorable prognostic factors included first and second vs. third and subsequent recurrences, high Karnofsky Performance Score (KPS) and no prior bevacizumab use. No unexpected adverse events were detected in PRiDe. As in the EF-11 trial, the most frequent adverse events were mild to moderate skin reactions associated with application of the Optune transducer arrays.

Pivotal Clinical Study in Recurrent GBM¹

Study Design: The study was a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of recurrent GBM subjects treated with Optune to those treated with an effective best standard of care (BSC) chemotherapy (including bevacizumab).

The following were the objectives of the study:

- To prospectively compare the median overall survival of recurrent GBM subjects treated with Optune to those treated with best standard of care (BSC) active chemotherapy
- To prospectively determine PFS6, TTP, 21-year survival and quality of life of subjects treated with Optune compared to BSC
- To collect evidence of the safety of 11 fields applied to subjects with recurrent GBM using Optune

Eligibility Criteria: The inclusion and exclusion criteria for the trial were as follows

Inclusion Criteria

- a. Pathological evidence of GBM using WHO classification criteria
- b. ≥ 18 years of age
- c. Not a candidate for further radiotherapy or additional resection of residual tumor
- d. Subjects with disease progression (by Macdonald criteria (i.e. $> 25\%$ or new lesion) documented by CT or MRI within 4 weeks prior to enrollment
- e. Karnofsky score ≥ 70
- f. Life expectancy at least 3 months
- g. Participants of childbearing age must use effective contraception
- h. All subjects must sign written informed consent

Exclusion Criteria

- a. Actively participating in another clinical treatment trial
- b. Within 1 weeks from surgery for recurrence
- c. Within 4 weeks from any prior chemotherapy
- d. Within 4 weeks from radiation therapy
- e. Pregnant
- f. Significant co-morbidities within 4 weeks prior to enrollment:
 - 1) Significant liver function impairment AST or ALT > 3 times the upper limit of normal
 - 2) Total bilirubin $>$ upper limit of normal
 - 3) Significant renal impairment (serum creatinine > 1.7 mg/dL)
 - 4) Coagulopathy (as evidenced by PT or APTT > 1.5 times control in subjects not undergoing anticoagulation)
 - 5) Thrombocytopenia (platelet count $< 100 \times 10^3/\mu\text{L}$)
 - 6) Neutropenia (absolute neutrophil count $< 1 \times 10^3/\mu\text{L}$)
 - 7) Anemia (Hb < 10 g/L)
 - 8) Severe acute infection
- g. Implanted pacemaker, defibrillator or deep brain stimulator, or documented clinically significant arrhythmias
- h. Intracranial tumor
- i. Evidence of increased intracranial pressure (midline shift > 5 mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)

¹Stupp, R. et al. (2017) "NovoTIF 100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality." *Eur J Cancer* 40(14): 2192-207

Study Procedures:

Treatment Arm

At treatment initiation subjects were hospitalized for 24 hours. During this period baseline examinations were performed and Optune treatment was initiated by the investigator under continuous medical supervision. The subjects were also instructed by the investigator on the operation of Optune and battery replacement. Once the subjects were trained in operating the device they were released to continue treatment at home. The subjects received continuous Optune treatment. Treatment was discontinued in the case of non-compliance or clinical disease progression.

Control Arm

All subjects had baseline examinations performed prior to treatment initiation. Subjects received the best effective standard of care chemotherapy practiced at each of the participating centers. The effective BSC treatments used in the study were comprised mainly of the following chemotherapies: Platinum based chemotherapy (Carboplatin), Nitrosureas (BCNU), Procarbazine, lomustine and vincristine (PCV), TMZ, Bevacizumab, and Imatinib, erlotinib, irinotecan (mainly in Europe). Because these therapies were included in the trial as a group, no comparisons can be made to each individual chemotherapy regimen. Chemotherapeutic treatment protocol was according to standard procedures at each of the participating centers.

Follow-up

During treatment, and until progression for subjects who stopped treatment before progression, all subjects were seen once a month at an outpatient clinic where they underwent medical follow up and routine laboratory exams. An MRI was performed every 2 months until disease progression. Central MRI review was performed by a neuro radiologist blinded to the treatment group of each subject. Medical follow-up continued for 2 months following disease progression. Subject survival was assessed based on monthly telephone interviews with the subjects' caregivers.

Subject Characteristics: 237 subjects (120 Optune; 117 BSC) with progressive or recurrent GBM were enrolled in the study. Baseline characteristics were as follows: mean age: 53.6 years; mean Karnofsky score: 81.6±10.9%; tumor size (cm³): 16.2±12.4; progression number: 1.4±0.9; re-operated: 36%; male: 70%; previous low grade: 10%; prior bevacizumab failure: 19%. Baseline characteristics were similar between treatment groups with slightly more men in the Optune group than in the BSC group (77% vs. 62%), a lower incidence of frontal lobe tumors in the Optune group than in the BSC group (32% vs. 50%), and a slightly higher mean KPS in the Optune group than in the BSC group (83% vs. 80%), though the median KPS was 80 in both groups. Adjusted analyses for all pre-specified or all statistically significant baseline covariates for overall survival did not change the outcome of the trial.

Demographics and Baseline Characteristics (ITT)

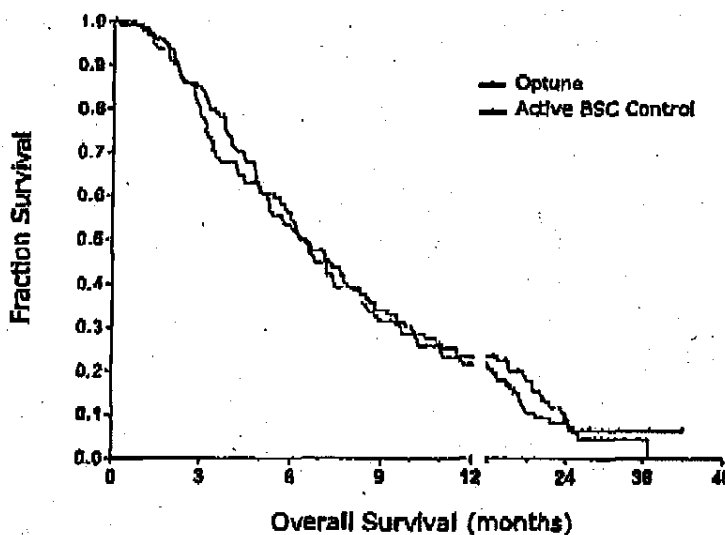
| Characteristics | Optune (N=120) | BSC (N=117) |
|-----------------------------------------------------------------|-------------------|----------------|
| | n (%) | n (%) |
| Caucasian | 111 (93) | 106 (91) |
| African American | 2 (2) | 5 (4) |
| Asian | 0 | 3 (3) |
| Hispanic | 7 (6) | 2 (2) |
| Other | 0 | 1 (1) |
| Female Gender | 28 (23) | 44 (38) |
| Frontal Tumor Position | 38 (32) | 58 (50) |
| Bilateral or Midline Tumor Location | 23 (19) | 17 (15) |
| Prior Avastin Use | 24 (20) | 21 (18) |
| Re-operation for Recurrence | 33 (28) | 29 (25) |
| Prior Low-grade Glioma | 12 (10) | 11 (9) |
| Median Age (years) (min, max) | 54 (24, 80) | 54 (29, 74) |
| Median Weight (kg) | 90 | 80 |
| Mean Number of Prior GBM Recurrences | 1.5 | 1.3 |
| Median Karnofsky Performance Score (min, max) | 88 (50, 100) | 80 (50, 100) |
| Median Tumor Area (mm ²) | 1440 | 1391 |
| Median Time from GBM Diagnosis to Randomization (days) | 334 | 340 |
| Mean Time from Last Radiotherapy Dose to Randomization (Months) | 13.71 | 13.93 |

Effectiveness Results:**Primary Effectiveness Endpoint: Overall Survival (ITT)**

In the ITT population which included all randomized subjects (Novo-TTF=120, BSC=117), overall survival in subjects treated with Optune was comparable to that observed in subjects treated with BSC (median OS=6.3 vs. 6.4 months; p=0.98). In the US, the median overall survival was 6.1 vs. 5.3 months in the ITT population. The pivotal study data establish that Optune therapy is comparable to BSC therapy in extending OS.

| | Treatment Group | |
|-----------------------|------------------|-----|
| | Optune | BSC |
| N | 120 | 117 |
| Median OS (months) | 6.3 | 6.4 |
| Log-rank p-Value | 0.98 | |
| Hazard Ratio (95% CI) | 1.00 (0.76-1.32) | |

The Kaplan-Meier survival curve for the two treatment groups appeared to be very similar during the first 12 months of follow-up, where 80% of the events occurred in both groups. Between 12 and 24 months, the survival curves separated slightly in favor of the BSC control group. However, after 12 months, the number of subjects remaining may be too small to reliably estimate the long term survival outcome.



| | Optune (N=120) | Active BSC Control (N=117) |
|---------------------------|----------------|----------------------------|
| Deaths | 105 | 97 |
| Censored | 15 | 20 |
| Lost to follow-up | 6 | 10 |
| Alive at end of follow-up | 9 | 10 |
| Median (months) | 6.3 | 6.4 |
| 95% Confidence Interval | 5.6, 7.8 | 5.2, 7.4 |

Correlation between Treatment Compliance and Overall Survival: Optune has an internal log file which allows the calculation of patient compliance with treatment. Significantly higher overall survival ($p=0.0447$) was observed in patients who were treated 75% or more of the time on average (OS=7.7 months) compared to patients treated less than 75% of the time on average (OS=4.5 months).

Secondary Effectiveness Endpoints: Secondary endpoint results support the findings in the primary endpoint. The one-year survival is similar in the Optune and BSC groups in the ITT population (21.9% vs. 22.1%). Progression free survival at 6 months (PFS6) is the same in the ITT population (21.4% vs. 15.2%). Radiological response rates from the subset of patients evaluated were reported as 14% for the Optune group compared to 9.6% for the BSC group in the ITT population. Median time to progression (TTP) was 9.3 weeks for Optune vs. 9.6 weeks for BSC.

| | Treatment Group | |
|--------------------------------|-----------------|-----------------|
| | Optune | BSC |
| N | 120 | 117 |
| 1-year survival | 21.9% 25/114 | 22.1% 25/104 |
| PFS6 (%) | 21.4% 22/103 | 15.2% 14/92 |
| Radiological Response Rate (%) | 14.0% 14/100 | 9.6% 7/73 |
| Median TTP (weeks) | 9.3 | 9.6 |

Quality of Life: Quality of life in subjects using Optune was better than those on BSC chemotherapy in most subscale domains, including vomiting, nausea, pain, diarrhea, constipation, cognitive and emotional functioning.

Safety Results: The characteristic adverse events of almost all chemotherapies are seen in a significantly higher proportion of BSC control subjects than in Optune subjects: gastrointestinal (30% vs. 8%), hematological (19% vs. 4%) and infectious (12% vs. 4%). Mild to moderate skin irritation beneath the device transducer arrays was observed in 16% of Optune subjects; none of these cases were assessed as severe by the investigator, all resolved after discontinuing treatment, and all were treated with topical steroids and periodic shifting of transducer array positions.

Number of Patients with Adverse Events by Body System (>2%)

| System Organ Class | Optune | BSC Chemotherapy |
|------------------------------------------------------|------------|------------------|
| | N=116 (%) | N=91 (%) |
| Blood and lymphatic disorders | 5 (4.3%) | 17 (18.7%) |
| Gastrointestinal disorders | 9 (7.8%) | 27 (29.7%) |
| General disorders and administration site conditions | 15 (12.9%) | 14 (15.4%) |
| Infections and infestations | 5 (4.3%) | 11 (12.1%) |
| Injury, poisoning and procedural complications | 21 (18.1%) | 1 (1.1%) |
| Metabolism and nutrition disorders | 9 (7.8%) | 12 (13.2%) |
| Nervous system disorders | 50 (43.1%) | 33 (36.3%) |
| Psychiatric disorders | 12 (10.3%) | 7 (7.7%) |
| Respiratory, thoracic and mediastinal disorders | 7 (6.0%) | 10 (11.0%) |

Conclusions: Optune is a portable, battery operated device which delivers TTFs to patients with recurrent GBM. The results of the pivotal trial showed that Optune subjects had comparable overall survival to subjects receiving the best available chemotherapy in the US today (OS 6.3 vs. 6.4 months; HR 1.0; p=0.98). Similar results showing comparability of Optune to BSC chemotherapy in the ITT population were seen in all secondary endpoints.

Optune subjects experienced fewer adverse events in general, significantly fewer treatment related adverse events, and significantly lower gastrointestinal, hematological and infectious adverse events compared to BSC controls. The only device-related adverse event seen was a mild to moderate skin irritation beneath the device transducer arrays, which was easily treated with topical ointments. Finally, certain quality of life measures were better in Optune subjects as a group when compared to subjects receiving effective BSC chemotherapy.

Directions for Use

Detailed directions for use for Optune can be found in:
The Optune Patient Information and Operation Manual

Abbreviations

AE – Adverse event

BSC – Best standard of care (effective chemotherapies)

GBM – Glioblastoma Multiforme (Glioblastoma, Astrocytoma grade IV), the most common and anaplastic primary brain tumor

ITT – Intent-to-Treat. This analysis population includes all randomized subjects.

kHz – kilo hertz; number of cycles per second

Optune– A portable battery, or power supply, operated device for delivering 200 kHz TTFields to the brain of patients with recurrent GBM

OS – Overall survival

PP – Per Protocol. This analysis population includes all patients who received at least the first course of TMZ and had no major protocol deviations.

PFS – Progression free survival

PFS6 – Proportion of patients alive and progression free at 6 months from randomization

Radiological Response Rate – sum of complete and partial radiological response rates

TMZ – a type of cancer drug used to treat newly diagnosed GBM

TTFields – Tumor Treating Fields: Low intensity (1-3 V/cm), intermediate frequency (100-300 kHz), alternating electric fields, delivered using insulated transducer arrays to the region of the body afflicted with a solid tumor. The fields have been shown in vitro to arrest the replication of tumor cells by disrupting the proper formation of the microtubule spindle and by dielectrophoretic disruption of cell integrity during late telophase

TTP – Time to progression

V/cm – Volts per centimeter; the unit of intensity measurement of electric fields

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The following abstract will be presented on Saturday, November 15, 2014, at 11:40am at the 19th Annual Scientific Meeting of the Society for Neuro-Oncology. The information below is embargoed until 8:00am, Saturday, November 15, 2014.

Interim Analysis of the EF-14 Trial: A Prospective, Multi-center Trial of NovoTTF-100A Together With Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM

Roger Stupp, Eric Wang, Charles Scott, Sophie Taillibert, Andrew Kanner, Santosh Kesari and Zvi Ram on behalf of the EF-14 Trial Investigators

BACKGROUND: Tumor Treating Fields (TTFields) are an anti-mitotic, physical treatment modality that acts in metaphase, anaphase and telophase. The NovoTTF-100A System (NovoTTF), a home-use medical device that delivers TTFields to the brain, is an established monotherapy for recurrent glioblastoma (GBM).

METHODS: We conducted an international, multicenter, prospective, randomized phase III trial in newly diagnosed GBM patients. After completion of radiotherapy (RT) with concomitant temozolomide (TMZ), patients were randomized (2:1) to adjuvant TMZ with NovoTTF or adjuvant TMZ alone. The primary endpoint was progression-free survival (PFS), with overall survival (OS) an important secondary endpoint. Here we report on a pre-specified interim analysis of the first 315 patients randomized, after a minimum follow-up of 18 months (range 18-60 months).

RESULTS: (Intent-to-treat): 210 pts were randomized to NovoTTF/TMZ and 105 to TMZ alone. Patient characteristics were balanced: median age 57 and 56 years, tumor resection in 89 and 90%, KPS 90%, for the NovoTTF and the control arms, respectively. MGMT promoter methylation status was assessable centrally in 50% of patients; of these 39% and 41% were methylated. Adverse events (AE) were comparable between treatment arms. The most common device-related AE was skin irritation in 45% of patients (all grades, severe 2%). Severe seizures were observed at a frequency of 7% in both arms. Median PFS was 7.1 months (mo) (95% confidence interval [CI] 5.9-8.2) and 4.0 mo (CI 3.0-4.3; Hazard ratio 0.63, $p=0.001$), OS was 19.6 mo (CI 16.5-24.1) and 16.6 mo (CI 13.5-19.1) (HR 0.75, $p=0.034$), both favoring NovoTTF. This translates into a 24-mo survival rate of 43% (CI 36-50%) and 29% (CI 21-39%) for the NovoTTF/TMZ and the TMZ alone arm, respectively.

CONCLUSIONS: The trial met its primary and main secondary endpoints, and was closed to accrual after this interim analysis. Adjuvant TMZ chemotherapy and NovoTTF provides a clinically and statistically significant improvement in progression-free and overall survival, and should become the new standard of care against GBM.

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Medicare & Medicaid Services
7500 Security Boulevard, Mail Stop C5-08-27
Baltimore, Maryland 21244-1850



Center for Medicare

Refer to: FCHBB

JUL 26 2013

James C. Stansel
Sidley Austin LLP
1501 K Street, NW
Washington, DC 20005

Dear Mr. Stansel:


Thank you for your inquiry requesting an informal benefit category determination (BCD) for the NovoTTFTM-100A System.

According to your letter and the information you provided during the meeting with Centers for Medicare and Medicaid Services (CMS) on May 21, 2013, the NovoTTFTM-100A System is a non-invasive system used in the patient's home that delivers tumor treating fields therapy to the brain to disrupt rapid cell division exhibited by recurrent GBM tumors. The NovoTTFTM-100A System is comprised of a durable electrical field generator and disposable insulated transducer arrays for use with the Generator. The System also includes lithium ion batteries, battery rack, battery charger, power supply, connection cables, and a carrying case. The NovoTTFTM-100A System received pre-market approval (PMA) from FDA in April 2011 for recurrent GBM.

In order for an item to be covered by Medicare, it must meet the definition of a Medicare-covered benefit. However, it is important to note that although Medicare provides coverage for certain items, it does not provide coverage for every item that may be useful to a person with a medical problem, even if a physician prescribes the item. The Medicare definition of durable medical equipment (DME) includes equipment which: can withstand repeated use; has an expected life of at least three years; is primarily and customarily used to serve a medical purpose; generally is not useful to a person in the absence of an illness or injury; and is appropriate for use in the home.

Based on the product information we reviewed, we believe that the NovoTTFTM-100A System falls within the DME benefit category. I hope that this information is helpful to you.

Sincerely,


Joel E. Kaiser
Director
Division of DMEPOS Policy

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OPTUNE™
(FORMERLY NOVOTTF™-100A SYSTEM)

CLINICAL DOSSIER

TUMOR TREATING FIELDS THERAPY

Treatment for Glioblastoma Multiforme

Page 1 of 30

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List of Abbreviations and Definitions of Terms

AE – Adverse Event

BCNU – Carmustine, chemotherapy

BPC – Best Physician Choice

BSC – Best Standard Care

c – Centigrade

CCNU – Lomustine (CeeNU), chemotherapy

CE Mark -- Conformité Européenne mark, for products sold in the European Economic Area

CI – Confidence Interval

cm – Centimeters

DTIC -- Dacarbazine

dAEs -- Dermatologic adverse events

ECG – Electrocardiogram

EMC -- Electromagnetic Compatibility

F-98 – Rat glioblastoma cell line

FDA -- Food and Drug Administration

GBM – Glioblastoma Multiforme (Glioblastoma, Astrocytoma grade IV), the most common and anaplastic primary brain tumor

Gy – Gray, unit of radiation

HR – Hazard Ratio

ITT – Intent-to-Treat

INE – Insulated Electrical Array

kHz – Kilo Hertz; number of cycles per second

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KPS – Karnofsky Scale

mHz – Mega Hertz, number of cycles per second

MGMT – 06-methylguanine-DNA methyltransferase

MITT – Modified intention-to-treat

mo. -- Months

MRI -- Magnetic Resonance Imaging

ORR - Objective Response Rate

OS – Overall Survival

PCV – Procarbazine, CCNU and vincristine-combination chemotherapy

PFS – Progression Free Survival

PFS6 – Progression Free Survival at 6 months

PMA – Pre-market Approval

PRiDe -- Patient Registry Dataset

QOL – Quality of Life

RR – Radiological Response Rate--Sum of complete and partial radiological response rates

TENS -- Transcutaneous Electrical Nerve Stimulation

TMZ--Temozolomide

TTFields – Tumor Treating Fields: Low intensity (1-3 V/cm), intermediate frequency (100-300 kHz), alternating electric fields, delivered using insulated transducer arrays to the region of the body afflicted with a solid tumor. The fields have been shown to arrest the replication of tumor cells by disrupting the proper formation of the microtubule spindle and by dielectrophoretic disruption of cell integrity during late telophase.

U-87 - Human glioblastoma cell line

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US -- United States

V/cm -- Volts per centimeter; the unit of intensity measurement of electric fields

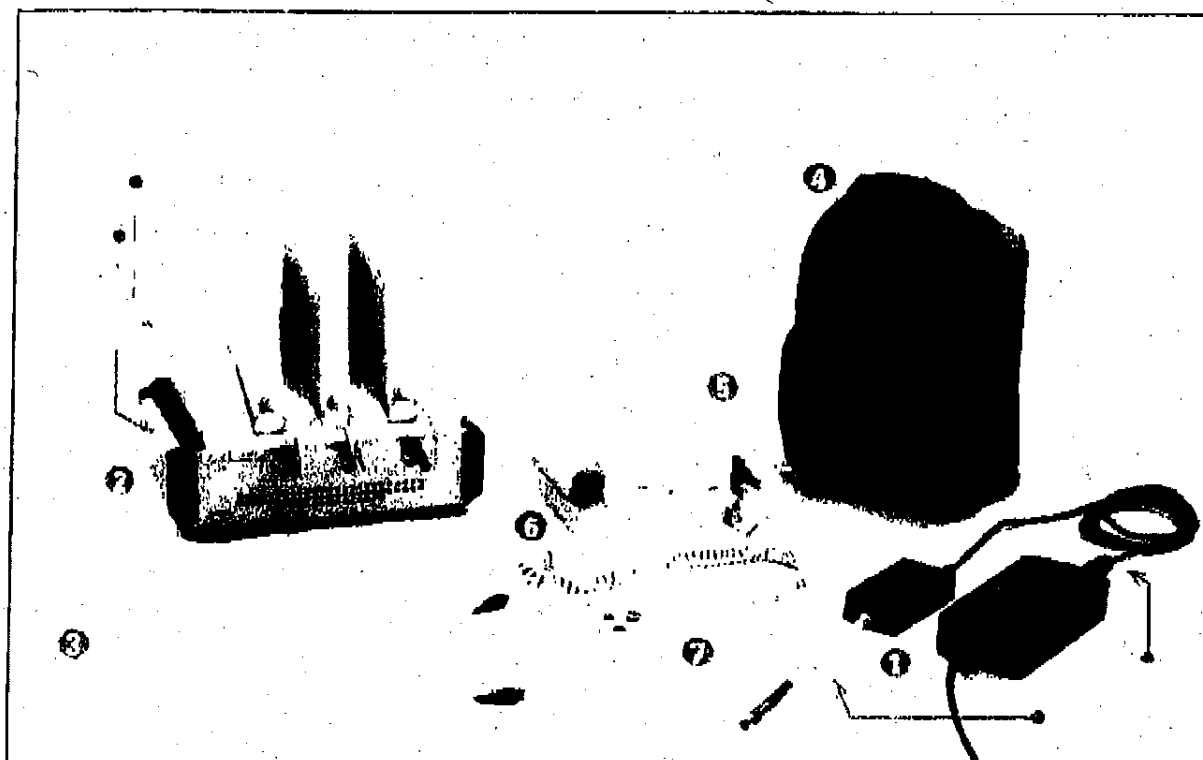
WHO -- World Health Organization

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Figure 1. Optune Treatment Kit



- 1 Plug In Power Supply
- 2 Charger for Portable Batteries
- 3 Transducer Arrays
- 4 Device & Battery Carrying Bag
- 5 Electric Field Generator (the Device)
- 6 Portable Battery
- 7 Connection Cable & Box

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Figure 2. Use of Device Overview



1. Prepare scalp.



2. Remove four transducer arrays from package.



3. Place transducer arrays on scalp.



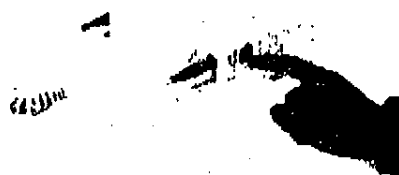
4. Connect transducer arrays to connection cable & device. Match colored rings to color coded sockets.



5. Place device and battery in bag (if applicable) and connect battery or power supply.



6. Connect connection cable to device.



7. Start treatment. Turn on power switch and push TTFields button.

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8. Place bag over shoulder.



9. Replace transducer arrays as needed.



10. Recharge batteries when not in use.

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1) Burden of Illness and Standard of Care for GBM

Glioblastoma multiforme (GBM), a malignant form of astrocytoma, is the most common and most aggressive form of primary brain cancer; but it remains a rare disease.

Burden of Illness

The incidence of GBM increases steadily above 45 years of age, with approximately 10,000 new cases annually in the United States. GBM tends to occur more frequently in males than females by a ratio of about 3:2. The outcome of patients with this disease has not improved significantly in recent years, despite the introduction of improved chemotherapies, including temozolomide (TMZ) (Merck; Temodar), bevacizumab (Roche, Avastin), and the use of GLIADEL® Wafers (carmustine). The 4-year survival of these patients is only 6.3% with a median overall survival (OS) of 14.6 months (Ostrom, 2015).

Nearly all patients with newly diagnosed GBM relapse within the first year despite aggressive treatment. Recurrent GBM is an end-stage condition; median OS from time of recurrence is approximately 3 to 5 months without additional effective treatment.

Quality of Life (QOL) for patients with GBM is generally poor due to the neurological deficits caused by the tumor itself together with the associated side effects of the various approved and experimental treatments.

Insurance Burden

To determine which US health insurers cover GBM patients, it is helpful to know that the median age at diagnosis is approximately 64 years. Therefore, the expected population for a private health care payer in the US is approximately 16 patients per 1 million covered lives (10,000 with GBM x 50% non-Medicare x 64% with private health care coverage = 3,200 divided by 201.1 million covered lives with private insurance = 16 lives per million covered).

Existing Treatment Options for GBM

There are currently four principal treatment options for GBM. Even with these treatments, the median time to recurrence of the tumor has been extended by only a few months. Once the tumor has recurred, patients have limited treatment options.

Newly Diagnosed GBM

Standard of care for a patient with newly diagnosed GBM and adequate functional status is debulking surgery, radiation with concurrent TMZ followed by adjuvant TMZ. Some elderly patients simply receive standard radiation or TMZ. Any or all of the following options may be pursued:

- **Surgical Resection** – Surgery to debulk the tumor and obtain tissue for diagnosis is the most common initial approach for newly diagnosed GBM. The surgical goal is to remove as much of the tumor as possible without

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compromising neurological function. When surgical resection is not feasible due to tumor location or patient's clinical condition, open or stereotactic biopsy may be performed.

- **GLIADEL® Wafer in Combination with Surgical Resection** – The GLIADEL® Wafer may be placed in the brain cavity at the time of surgical resection to deliver carmustine (BCNU) directly to the site of the brain tumor (interstitial chemotherapy). A modest increase in median survival has been shown over placebo (13.9 mo. vs. 11.6 mo.) when used in newly diagnosed GBM. Treatment with GLIADEL® wafer is associated with the following common side effects (incidence >10% and between arm difference ≥4%): cerebral edema, asthenia, nausea, vomiting, constipation, wound healing abnormalities and depression.
- **Radiation Therapy – Localized radiotherapy is typically given over a six-week period following surgical resection with a total dose of approximately 60 grays (Gy).** Side effects of radiation therapy depend on the type of radiation received, the amount of the surface of the brain targeted, the site targeted, and the total dose of radiation. In general, there will be hair loss, skin irritation, possible hearing problems, nausea, vomiting, loss of appetite, and neurologic effects. The most prevalent side effect is fatigue, which may last through treatment and for many months afterwards.
- **Cytotoxic Chemotherapy – TMZ, an oral alkylating agent, is administered concomitant with radiation therapy and continued for a minimum of six months following radiation.** Significantly improved OS and median survival have been demonstrated in large trials. Recent studies have shown that patients with methylated O6-methylguanine-DNA methyltransferase (MGMT) may have a superior response to TMZ therapy. Side effects from TMZ therapy include: nausea, vomiting, loss of appetite, constipation, tiredness, and headache. Temporary loss of hair also can be expected.

Recurrent GBM

There is little data on effective strategies for treatment of recurrent GBM.

- **Surgical Resection** – Repeat surgery for GBM at the time of tumor recurrence may be offered when it is feasible although there is no data indicating that it offers significant survival benefit. Second surgery is considered in only about 20% of patients.
- **GLIADEL® Wafer in Combination with Surgical Resection** – Use of GLIADEL® Wafer is limited to selected cases undergoing additional surgical resection for recurrent GBM. The package insert indicates that for recurrent GBM, GLIADEL® Wafer increased median OS from 4.6 to 6.5 months compared to placebo.

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- **Radiation Therapy** - Because the full standard dose of radiation (60 Gy) typically is given after initial diagnosis with GBM, irradiation for disease recurrence may not be possible. However, with advances in technology, re-irradiation with fractionated stereotactic radiotherapy can provide survival benefit.
- **Cytotoxic Chemotherapy** - There is no established standard treatment for recurrent GBM. Chemotherapy treatment strategies are ill-defined, with several different preferred regimens. The most common are: nitrosureas, (BCNU), procarbazine, PCV (procarbazine, CCNU and vincristine), and platinum based (e.g. carboplatin). None of these agents is FDA approved specifically for recurrent GBM. Most patients suffer from combinations of unpleasant and sometimes life-threatening side effects of their chemotherapeutic treatments,
- **Bevacizumab (Avastin)** may be used as monotherapy for patients with recurrent GBM (Cohen, 2009). The FDA approval was based on two phase 2, single arm trials comparing bevacizumab to historical control data. Benefit was seen in objective response (OR) rates and progression free survival at six month (PFS6) compared to historical control data. OS was shown to be between 8 to 9 months however, an OS claim is not made in the approved labeling

In summary, despite an aggressive initial standard of therapy treatment, most GBM patients develop recurrent disease. When tumors recur, only 20% of patients are eligible for additional resection. There is a high unmet need for therapies to treat recurrent GBM.

2] Description and Use of Optune

Overview

Optune is a portable, wearable medical device, which produces alternating electrical fields, tumor treating fields or "TTFields," within the brain by means of electrically-insulated surface transducer arrays placed on the scalp. The TTFields are believed to disrupt the rapid cell division exhibited by cancer cells.

Indication for Use:

Optune™ is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme. (GBM)

Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy

For the treatment of recurrent GBM, Optune™ is indicated following histologically-or radiologically-confirmed recurrence in the supratentorial region of the brain after

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receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options

Summary of Important Safety Information:

Contraindications

Do not use Optune if you have an active implanted medical device, a skull defect (such as, missing bone with no replacement), or bullet fragments. Use of Optune together with implanted electronic devices has not been tested and may theoretically lead to malfunctioning of the implanted device. Use of Optune together with skull defects or bullet fragments has not been tested and may possibly lead to tissue damage or render Optune ineffective.

Do not use Optune if you are known to be sensitive to conductive hydrogels. In this case, skin contact with the gel used with Optune may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings and Precautions

Use Optune only after receiving training from qualified personnel, such as your doctor, a nurse, or other medical personnel who have completed a training course given by Novocure (the device manufacturer).

Do not use Optune if you are pregnant, you think you might be pregnant or are trying to get pregnant. It is not known if Optune is safe or effective in these populations.

The most common ($\geq 10\%$) adverse events involving Optune in combination with temozolomide were low blood platelet count, nausea, constipation, vomiting, fatigue, scalp irritation from device use, headache, convulsions, and depression.

The most common ($\geq 10\%$) adverse events seen when using Optune alone were scalp irritation from device use and headache.

The following adverse reactions were considered related to Optune when using the device alone: scalp irritation from device use, headache, malaise, muscle twitching, fall and skin ulcer.

All servicing procedures must be performed by qualified and trained personnel.

Do not use any parts that do not come with the Optune Treatment Kit, or that were not sent to you by the device manufacturer or given to you by your doctor.

Do not wet the device or transducer arrays.

If you have an underlying serious skin condition on the scalp, discuss with your doctor whether this may prevent or temporarily interfere with Optune treatment.

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System Components

Optune is comprised of two main components: 1) an Electric Field Generator (the "device") and 2) INE Insulated Transducer Arrays (the "arrays"). (See Figure 1 for illustration.)

- The device is portable, battery- or power supply-operated. It is connected to two pairs of array sets, which operate sequentially. The intensity of the field, the frequency of the waves, and the temperature of the transducer arrays are pre-set and monitored by the device. The device and battery weigh about six pounds together.
- The transducer arrays are disposable and approved for single use only. They are highly engineered, using military grade insulation that cannot withstand repeated use due to micro-cracks that form over time. The arrays are embedded with a precise temperature sensing technology to prevent skin burns. They are designed to deliver and monitor the therapy simultaneously while maintaining electrical insulation and patient safety. Due to their advanced engineering requirements and unique material composition, they contribute meaningfully to the device cost.

Additional Components: In addition to the device and transducer arrays, the Optune treatment kit includes a plug-in power supply, portable batteries, battery charger, connection cable, and carrying case. (See Figure 1 for illustration.)

Treatment Overview

Overview

The US FDA requires that the treating physician complete training and receive certification from the manufacturer prior to prescribing treatment with Optune. Additionally, nurses, nurse practitioners, physician's assistants, and any other health care professional providing direct patient care related to Optune must also have completed training and certification.

The manufacturer-provided training is designed to educate the prescribing physician and allied healthcare professionals on the scientific basis for Optune therapy, clinical information on the efficacy and safety of Optune, the process to interpret an MRI to determine the array layout plan, the training required for the patient, and also the steps to start and oversee treatment, including the process of assessing monthly compliance.

Transducer Array Layout Plan

The physician must plan the appropriate layout of the transducer arrays around the tumor location prior to starting treatment. This layout planning process requires a current patient MRI. Treatment planning determines the appropriate array placement to maximize Optune intensity within the tumor.

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Treatment Start

Treatment initiation often takes place in the patient home. The patient and caregiver receive device related training from a Novocure representative. The patient has his or her scalp shaved to ensure proper contact of the transducer arrays to the skin. The caregiver places the arrays in accordance with the prescribed array layout and initiates therapy by turning the device on. (See Figure 2 for illustration.)

Patient and Caregiver Training

Novocure representatives are responsible for training the patient and caregiver on the technical aspects and use of the device. All medical questions are referred back to patient's provider. This training involves technical training related to the device operation, including educating the patient on battery replacement, battery charging, using the power supply, connecting and disconnecting from the device, and on the appropriate placement of transducer arrays in accordance with the treatment plan. Additionally, the patient and caregiver will have access to a 24-hour technical support service offered by the device manufacturer.

Transducer Array Placements – After Successful Patient Training

The patient and caregiver, once properly trained, are expected to change the transducer arrays. The caregiver will be trained to shave the patient's scalp, maintain good skin care protocols, and to place the arrays in accordance with the prescribed treatment plan. The arrays are changed and the scalp is re-shaved about every three to four days to ensure contact with the skin. Patients know to change the arrays when the alarm beeps more often to signal the need for the change.

Monthly Treatment Assessment

Patients typically are scheduled to meet the physician once per month, exclusive of Optune treatment. The Novocure Representative will provide the physician a monthly compliance report which is reviewed with the patient during this appointment. The compliance log provides the physician with an overview of device usage by day and by time of day (day versus night). The physician uses this compliance log to encourage appropriate use of Optune. During this monthly appointment, the physician also reviews transducer array location to ensure appropriate placement in accordance with the prescribed treatment plan. If compliance is problematic, patients and caregivers may be retrained in the proper use of the device.

Device Use Overview

Treatment Duration

The physician-prescribed device is used for newly diagnosed patients in combination with temozolomide and as monotherapy for patients diagnosed with recurrent glioblastoma. Physicians may choose to keep patients on Optune at first recurrence. For maximum benefit, the recommended average daily use is at least 18 hours a day.

Device Settings

Novocure pre-sets all device treatment parameters; there are no programming adjustments available to the patient. The patient simply connects the device to an

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appropriate power supply (i.e., a charged battery or connection of the power supply to an electrical outlet) and turns it on and off.

Practical Considerations

Treatment may be interrupted for personal needs such as bathing or exercise. In order to take a shower, the patient must disconnect from the device (leaving the transducer arrays on the head), put on a shower cap, and be cautious not to get his/her head or any components of the device wet. Treatment also must be stopped to replace the arrays. When leaving the house, patients can put a wig or hat over the arrays, if desired.

Device Service

The device and batteries require frequent servicing. Novocure provides the patient with replacements for these components, as needed, and in most cases ships on an overnight basis. For minor technical issues, an alarm will sound to notify the patient. The patient manual has a simple troubleshooting guide that addresses the most common problems that may arise. In addition, Novocure has around-the-clock technical support. Patients are encouraged to call the Novocure technical support telephone number with questions about operations or device function.

FDA Approvals

The US Food and Drug Administration (FDA) approved Optune for use in newly diagnosed GBM in October 2015. (See FDA Approval Letter, Appendix A.)

Optune has been available for use in recurrent GBM since FDA approval (via premarket approval (PMA) pathway) in April 2011. (See FDA Approval Letter, Appendix A.)

Regulatory Approval Outside the United States

Optune is a CE Marked (Conformité Européenne) device cleared for sale in the European Union, Switzerland, Australia, Israel and Japan.

3] Optune Mechanism of Action

Background

The Optune System delivers tumor treating fields (TTFields) to the tumor. TTFields are intended to disrupt cancer cell division by utilizing the unique electrical and geometric properties of cells during the mitotic process.

Electric fields traditionally have been used in medicine in two different modes: 1) steady or low frequency electric fields (<1 kHz); and 2) high frequency alternating fields (>10 mHz). Steady or low frequency electric fields generate action potentials in excitable cells. These fields are used therapeutically in bone and soft tissue repair, pain control (TENS), and stimulation (neurologic or cardiac). In contrast, very high frequency

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alternating fields generate heat in the tissues by dielectric losses. Applications in therapeutic use include ablation, diathermy and hyperthermia.

In contrast, Optune harnesses intermediate frequency (200 kHz), low intensity (1-3 V/cm), alternating electric fields) to achieve its therapeutic effect. At this frequency and intensity, Optune cannot stimulate nerves or muscles or bone growth, nor do they heat the tumor or surrounding tissues. Since Optune is applied using electrically insulated arrays, there is no direct current flow into the tissue hence electrolysis and tissue damage do not occur. TTFields are delivered non-invasively via the arrays to GBM tumors using the Optune device.

Mechanism of Action

TTFields target two specific characteristics of cancer cells: the presence of electrically charged particles during mitosis and the geometrical shape of dividing cancer cells. TTFields have been shown to:

- inhibit cancer cell replication by interference with the proper formation of the mitotic spindle during metaphase and anaphase; and
- cause intracellular dielectrophoresis of macromolecule and organelles during cytokinesis.

Acting together, these two processes, which are specific to dividing cells only, may lead to apoptosis and can result in tumor arrest or regression *in vivo*.

In contrast, data indicate that Optune does not affect cells that are quiescent, that is, that are not dividing. Since most normal adult brain cells proliferate very slowly, if at all, scientists hypothesize that these cells are affected minimally by Optune. Additionally, the antimitotic effect of Optune has been shown to be frequency-specific to the cell type treated.

Optune application has the advantage of being locally-directed and is not expected to be associated with systemic toxicity.

4) Summary of Clinical Studies

Pilot and pivotal studies in both newly diagnosed and recurrent GBM have demonstrated that Optune is safe and effective in patients with GBM. The most recently completed study, EF-14 in newly diagnosed GBM, compared Optune in combination with maintenance TMZ compared to TMZ alone. The previous EF-11 trial for recurrent GBM compared Optune alone with best physician choice chemotherapy (BPC). To date, Optune therapy has been used in more than 2500 patients in the clinical as well as commercial setting. What follows is a synopsis of the EF-14 pivotal trial in newly

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diagnosed GBM and a summary of the published clinical study literature for both indications.

Newly Diagnosed GBM

A) EF-14 Pivotal Study

Overview

The EF-14 trial, as reported by Stupp et al. 2015, was a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of newly diagnosed GBM subjects treated with Optune and TMZ to those treated with TMZ alone. The multicenter, multinational (83 global centers) trial had a medium follow-up of 38 months (range 18 to 60 mo.). Sixty-one percent of study patients were from the US. Study endpoints were as follows:

Primary Endpoint: Progression-free survival (PFS) in the intent-to-treat population assessed by an independent review panel (significance threshold of .01)

Secondary Endpoint: Overall survival (OS) in the per-protocol (PP) population (significance threshold of .006)

Study Population

Patients with histologically confirmed GBM were recruited to the trial after completing maximal safe debulking surgery or biopsy, followed by radio-therapy in combination with TMZ chemotherapy.

Eligibility Criteria

Inclusion Criteria

- Pathological evidence of GBM using World Health Organization (WHO) classification criteria
- ≥ 18 years of age
- Received maximal debulking surgery and radiotherapy (45-70Gy) concomitant with TMZ
- Karnofsky scale ≥ 70
- Life expectancy at least 3 months
- Participants of childbearing age must use effective contraception.
- All patients must sign written informed consent.
- Treatment start date at least 4 weeks out from surgery.
- Treatment start date at least 4 weeks out but not more than 7 weeks from the later of last dose of concomitant TMZ.
- Treatment start date at least 4 weeks out from radiation therapy

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Exclusion Criteria

- Progressive disease (according to MacDonald Criteria¹).
- Actively participating in another clinical treatment trial
- Pregnant
- Significant co-morbidities at baseline which would prevent maintenance TMZ treatment:
 - Thrombocytopenia (platelet count $< 100 \times 10^3/\mu\text{L}$)
 - Neutropenia (absolute neutrophil count $< 1.5 \times 10^3/\mu\text{L}$)
 - CTC grade 4 non-hematological Toxicity (except for alopecia, nausea, vomiting)
 - Significant liver function impairment - AST or ALT > 3 times the upper limit of normal
 - Total bilirubin $>$ upper limit of normal
 - Significant renal impairment (serum creatinine > 1.7 mg/dL)
- Implanted pacemaker, defibrillator, deep brain stimulator, or documented clinically significant arrhythmia.
- Infra-tentorial tumor
- Evidence of increased intracranial pressure (midline shift > 5 mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)
- History of hypersensitivity reaction to TMZ or a history of hypersensitivity to dacarbazine (DTIC).

Study Procedure After completion of treatment with TMZ and radiotherapy, patients were randomized at a ratio of 2:1 to receive standard maintenance TMZ (150-200 mg/m²/d for 5 days every 28 days for 6-12 cycles) with or without the addition of Optune. The web-based randomization was stratified by extent of resection and MGMT methylation status.

Treatment Arm: Optune was given together with maintenance TMZ. At treatment initiation, patients were seen at an outpatient clinic. During this visit, patients received baseline examinations and Optune treatment was initiated. The patients were instructed on the operation of Optune and battery replacement. Once the patients were trained in operating the device, they were released to continue treatment at home. Following radiological progression or unacceptable toxicity, TMZ could be replaced with BSC second line chemotherapy. However, Optune could be continued until the second radiological progression, or clinical deterioration, for a maximum of 24 months.

¹ The Macdonald criteria divides response into 4 types of response based on imaging (MRI) and clinical features: complete response; partial response; stable disease; progression.

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Control Arm: All subjects had baseline examinations performed prior to treatment initiation. Patients were treated with maintenance TMZ according to the standard dosing regimen. Following radiological progression or unacceptable toxicity, TMZ could be replaced with BSC second line therapy.

Follow Up: During treatment, all patients were seen once every month at an outpatient clinic where they underwent medical follow-up and routine laboratory exams. Treatment adherence with Optune was recorded by the device, then reviewed and transferred at follow-up visits. A magnetic resonance imaging (MRI) was performed every second month following the baseline MRI until second progression or 24 months (whichever came first), when treatment on both arms of the study was terminated. In the case of clinical progression, an unscheduled MRI was obtained within 1 week after the investigator became aware of the clinical progression. No additional MRIs were required after second progression. Central MRI review was performed by an independent radiologist blinded to the treatment group of each patient. Medical follow-up continued for 2 months after treatment termination in order to capture treatment related toxicities. After these visits, mortality was assessed based on monthly telephone interviews with the patients or the patients' caregivers.

Study Patients: The study enrolled 695 of the 700 planned patients between July 2009 and November 2014; Optune/TMZ (n = 466) or TMZ alone (n = 229). Data from the prespecified Interim analysis of the first 315 patients with a minimum of 18 months of follow-up included 210 patients in the Optune plus TMZ arm and 105 in the TMZ alone arm. Baseline characteristics were well balanced in both groups. (See Appendix B) An independent data and safety monitoring committee review of the interim data determined that the predefined improvement in PFS and OS had been met and recommended termination of the study. Following FDA approval of the termination, the study was closed to recruitment and patients in the control group were allowed to crossover and receive Optune. A total of 35 patients crossed over. Follow-up for all patients continues; final analysis data are not expected before the end of 2016. The results that follow here are from the interim analysis.

Analysis Populations: PFS was analyzed in the intent-to-treat (ITT) population, which included all randomized subjects (Optune/TMZ=210; TMZ alone=105 at the interim analysis). OS was analyzed in the PP population which excluded all patients who 1) never started TMZ maintenance therapy, 2) had major protocol violations, 3) crossed over to the other treatment group, or 4) received Optune outside the protocol (Optune/TMZ=196; TMZ alone=84).

Treatment Delivery

The median number of TMZ cycles until evidence of first tumor progression was 6 cycles (range, 1-26 cycles) for patients in the Optune plus TMZ arm and 4 cycles (range, 1-24 months) in the TMZ arm alone. The median duration of treatment with Optune was 9 months (range, 1-58 months). Two-thirds of patients in the Optune plus TMZ arm continued treatment with TTFields after first tumor progression. Three-quarters of

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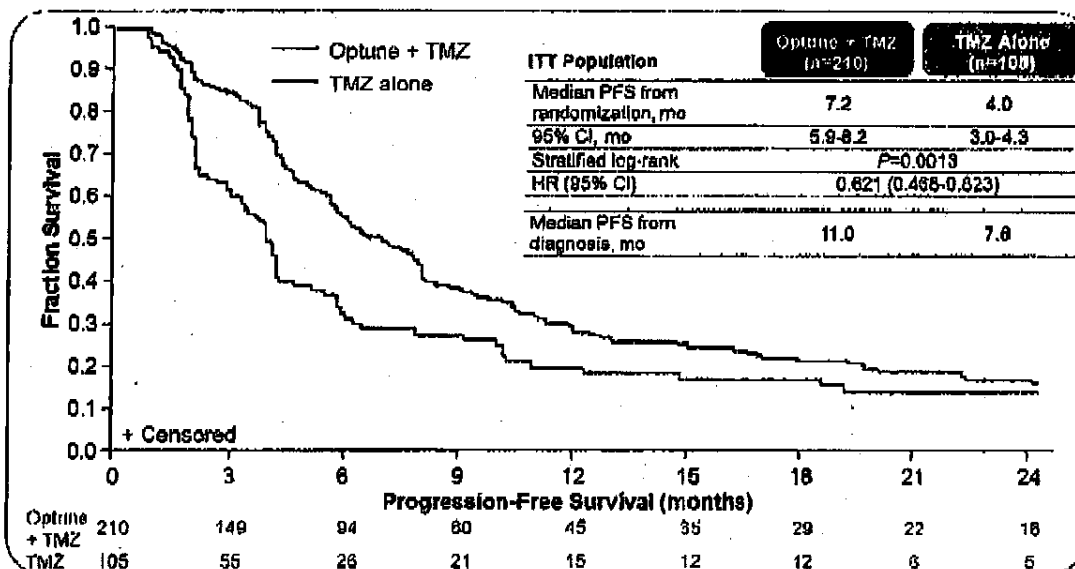
patients receiving Optune complied with therapy, wearing the device >18 hours per day on average for the first 3 treatment months.

Effectiveness Results:

Primary Effectiveness Endpoint: Progression Free Survival--ITT Population

The threshold for statistical significance of PFS at the interim analysis was pre-defined as an α level of .01 using a stratified log-rank test. PFS at the interim analysis met this threshold. After a median follow-up of 38 months (range, 18-60 months), the median PFS from randomization was 7.1 months (95% CI, 5.9-8.2 months) in the Optune plus TMZ arm compared with 4.0 months (95% CI, 3.3-5.2 months) in the TMZ only arm. Thus, the addition, of Optune to BSC TMZ extended median PFS by 3.1 months. (See Figure 3.)

Figure 3. Progression Free Survival: ITT Population



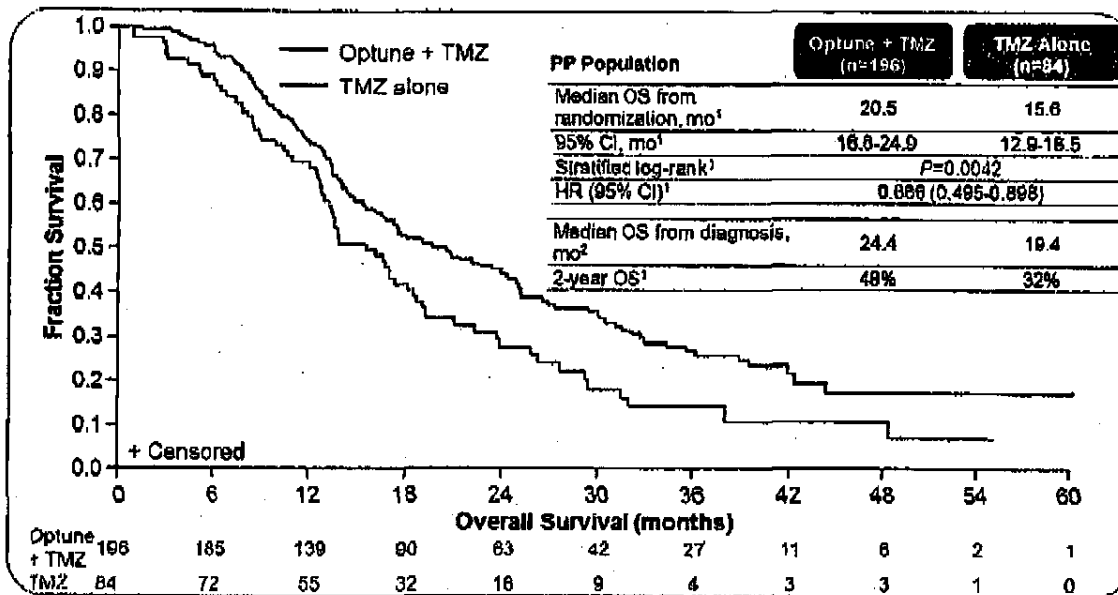
Secondary Effectiveness Endpoint: Overall Survival--PP population

OS was a powered secondary analysis in the trial and was to be tested only after the primary endpoint was found to surpass the threshold for significance in the interim analysis. The threshold for superior OS at the interim analysis was predefined in the protocol as an α level of .006 using a stratified log-rank test and was to be tested in the PP population (Optune/ TMZ = 196, TMZ alone = 84). Median OS in the PP population was 20.5 months (95%CI, 16.7-25.0 months) in the Optune plus TMZ arm compared with 15.6 months (95%CI, 13.3-19.1 months) in the TMZ alone arm.

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Figure 4. Overall Survival: PP Population



In an additional survival analysis of the ITT population, median OS was 19.6 months (95% CI, 16.6-24.4 months) in the Optune plus TMZ arm compared with 16.6 months (95% CI, 13.6-19.2 months) in the TMZ alone arm. Further, the percentage of patients alive at 2 years following enrollment was 43% in the Optune plus TMZ arm compared with 29% in the TMZ alone arm.

Robustness Analysis: To assess the robustness of the interim analysis findings, additional analyses on all 695 patients randomized were performed. Baseline characteristics of all patients randomized were similar to the interim data set as were the results for the main endpoints. PFS in the ITT population was 7.1 months (95% CI, 6.1-8.13 months) for the Optune plus TMZ arm and 4.2 months (95% CI, 3.93-5.87 months) for the TMZ alone arm. OS in the ITT population also favored Optune treated patients with a median of 19.4 months (95% CI, 16.6-23.9 months) vs. 16.6 months (95% CI, 13.9-18.6 months).

Safety Results: The addition of Optune to TMZ in patients with newly diagnosed GBM was not associated with any significant increase in systemic toxic effects compared with TMZ alone. (See **Appendix C**) However, patients receiving Optune did experience a higher incidence of localized skin toxicity (medical device reaction beneath the transducer arrays). Mild to moderate skin irritation was observed in 43% of patients treated with Optune plus TMZ and severe skin reaction (grade 3) noted in 2%. Skin reactions could be managed by using published skin care guidelines for patients receiving Optune. Mild anxiety, confusion, insomnia and headaches were reported more frequently in patients treated with Optune plus TMZ and occurred mainly at the time of therapy initiation. The incidence of seizures was 7% for the Optune plus TMZ arm and

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8% in the TMZ alone arm. Twelve patients died of causes considered to be unrelated to treatment, 8 (3.9%) in the Optune plus TMZ arm and 4 (4.0%) in the TMZ alone arm.

Conclusions: Results of the interim analysis of the pivotal trial in newly diagnosed GBM show that Optune plus TMZ significantly extends PFS and OS compared to patients receiving TMZ alone. The addition of Optune to BSC TMZ was shown to be safe; no significant increase in serious AEs was seen when Optune treatment was added to TMZ. The most common ($\geq 10\%$) adverse events involving Optune in combination with TMZ were low blood platelet count, nausea, constipation, vomiting, fatigue, scalp irritation from device use, headache, convulsions, and depression.

Recurrent GBM

B) EF-11 Pivotal Study

Stupp et al. (2012) published data from the EF-11 trial, a prospective, multicenter, randomized, active controlled clinical trial designed to compare the safety and effectiveness outcomes of recurrent GBM patients treated with Optune to those treated with BPC chemotherapy (including bevacizumab) selected by the treating physician. A total of 237 patients were enrolled in the study from 28 clinical centers in the US and Europe. The final study analysis compared 120 Optune patients with 117 BPC chemotherapy patients.

The study objectives were:

- To prospectively compare the OS of recurrent GBM patients treated with Optune to those treated with BPC chemotherapy.
- To prospectively determine the median survival, percent one-year survival rate, PFS, PFS6, RR rate and QOL of patients treated with the Optune compared to BPC chemotherapy.
- To collect evidence of the safety of Optune for patients with recurrent GBM using Optune.

Patients with previously diagnosed GBM who had relapsed or progressed despite conventional therapy (surgery and chemo-radiotherapy followed by chemotherapy) were recruited into the study. More than 80% of patients had failed two or more prior lines of chemotherapy and 20% had failed bevacizumab prior to enrollment, a population that usually fares poorly with subsequent treatments. Patients in the treatment arm received continuous Optune treatment at home while maintaining normal daily activity. Chemotherapy treatments used in the control arm were comprised mainly of the following as single agents or in combination: bevacizumab (Avastin) or irinotecan

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(mainly in Europe) followed by nitrosureas (BCNU), platinum based chemotherapy (carboplatin), and TMZ. Patients were seen monthly and had an MRI every two months until disease progression. Mean use of Optune was 20.6 hours per day.

Study results are summarized below.

- The pivotal study data establish that Optune therapy is at least comparable to chemotherapy in extending OS for patients with recurrent GBM; 6.6 months vs. 6.0 months.
- The secondary effectiveness endpoint results support the findings of the primary endpoint; they show the Optune device is at least clinically equivalent to active chemotherapy. In summary: PFS for treatment arm was 2.2 mo. vs. 2.1 mo.; PFS6 was 21.4% vs. 15.1%; and radiological response rate (RR) rate was 14.0% vs. 9.6%.
- QOL for patients treated with Optune is significantly improved compared to patients treated with active chemotherapies. Patients in the study arm reported improved cognitive, emotional and role functioning, and a marked improvement in adverse treatment-related symptoms such as nausea and pain.
- In a clinical trial, Optune was shown to be safe and well tolerated with significantly less toxicity than existing treatment options for recurrent GBM. The most common ($\geq 10\%$) adverse events seen when using Optune alone were scalp irritation from device use and headache. The following adverse reactions were considered related to Optune when using the device alone: scalp irritation from device use, headache, malaise, muscle twitching, fall and skin ulcer.

Conclusion: The pivotal study data established that Optune produces clinically comparable outcomes to BPC chemotherapy, including bevacizumab (Roche; Avastin), across both primary OS and secondary effectiveness end-points for recurrent GBM patients. Additionally, Optune therapy results in fewer treatment related adverse events and certain QOL measures were better with Optune than compared to BSC chemotherapy.

C] Patient Registry Dataset (PRiDe)

Mrugala et al (2014) report on PRiDe a post-marketing registry of patients who received Optune Therapy for recurrent GBM in the U.S. between October 2011 and November 2013. Data were collected from all 457 recurrent GBM patients who began commercial treatment during that period. Age and gender characteristics were similar in the PRiDe and EF-11 trial. OS was collected using the Social Security Death Date Registry and obituaries. Subgroup analyses were performed on patient/clinical characteristics and found to be significantly correlated with OS. A monthly compliance assessment was

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performed for each patient using a computer download of an internal log file from the Optune device.

Study findings include the following:

- Median OS for those on Optune therapy was significantly longer in PRiDe than in the EF-11 trial (9.6 mo. vs. 6.6 mo.)
- One- and two-year OS rates for Optune therapy patients were more than double in PRiDe as compared to the EF-11 trial (1-year- 44% vs. 20%; 2-year- 30% vs. 9%).
- No new adverse events were detected in PRiDe. The most common device-related adverse event was a skin irritation beneath the transducer arrays, easily treated with topical corticosteroids.

Major median OS differences in patients registered in PRiDe compared to median OS of those treated with Optune monotherapy in the EF-11 trial led to subgroup analyses to explore reasons for the variation. These analyses suggest there may be several favorable prognostic factors that influence OS in Optune-treated patients. These include: daily compliance $\geq 75\%$, Optune therapy initiated at first recurrence, use in Bevacizumab naive patients, and KPS ≥ 90 .

Conclusion: Understanding favorable prognostic factors may assist in appropriate patient selection for Optune

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Appendix A

FDA Approval Letters

Newly Diagnosed GBM

http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034S013a.pdf

Recurrent GBM

http://www.accessdata.fda.gov/cdrh_docs/pdf10/p100034a.pdf

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Appendix B

EF-14 Pivotal Trial Interim Analysis Patient Characteristics

| ITT Population | Optune + TMZ (n=210) | TMZ Alone (n=105) |
|---------------------------------------------------------|-------------------------|----------------------|
| Characteristics | | |
| Median age, years (range) | 57 (20-83) | 58 (21-80) |
| Female sex, n (%) | 70 (33) | 38 (36) |
| Median KPS (range) | 90 (60-100) | 90 (70-100) |
| Extent of resection, n (%) | | |
| Gross total resection | 135 (64) | 67 (64) |
| Partial resection | 52 (25) | 27 (26) |
| Biopsy | 23 (11) | 11 (10) |
| MGMT status, n (%) | | |
| Methylated | 49 (23) | 26 (25) |
| Unmethylated | 78 (38) | 38 (36) |
| Insufficient for testing | 24 (11) | 11 (10) |
| Not assessed | 58 (28) | 30 (29) |
| Median time from diagnosis to randomization, mo (range) | 3.8 (2.0-5.7) | 3.8 (1.4-5.7) |
| Duration of Therapy | | |
| Median number of TMZ cycles, n (range) | 6.0 (1-26) | 4.0 (1-24) |
| Median number of Optune cycles, n (range) | 9.0 (1-58) | 0 (0-0) |

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Appendix C Pivotal Trial Adverse Events—Interim Analysis Population

| Safety Population | Optune + TMZ (n=437) n (%) | TMZ Alone (n=207) n (%) |
|-------------------------------------------------------------|----------------------------------|-------------------------------|
| System Organ Class | | |
| Blood and lymphatic system disorders | | |
| Thrombocytopenia | 32 (7) | 10 (5) |
| Leukopenia | 8 (2) | 1 (<1) |
| Lymphopenia | 14 (3) | 7 (3) |
| Neutropenia | 8 (2) | 3 (1) |
| Anemia | 5 (1) | 4 (2) |
| General disorders and administration site conditions | | |
| Fatigue | 15 (3) | 7 (3) |
| Asthenia | 7 (2) | 1 (<1) |
| Procedural complications | | |
| Fall | 8 (2) | 1 (<1) |
| Nervous system disorders | | |
| Headache | 10 (2) | 3 (1) |
| Convulsion | 19 (4) | 11 (5) |
| Cognitive disorder | 4 (1) | 4 (2) |
| Hemiparesis | 9 (2) | 1 (<1) |
| Brain edema | 9 (2) | 8 (3) |
| Cerebral hemorrhage | 0 (0) | 4 (2) |
| Respiratory disorders | | |
| Pulmonary embolism | 8 (2) | 7 (3) |

- The most common (≥10%) adverse events involving Optune in combination with TMZ were thrombocytopenia, nausea, constipation, vomiting, fatigue, medical device site reaction, headache, convulsions, and depression

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Clinical Practice Experience With NovoTTF-100A™ System for Glioblastoma: The Patient Registry Dataset (PRiDe)

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John L. Villano,^f Daniela Annenelie Bota,^g Jeremy Rudnick,^h Ashley Love Sumrall,ⁱ
Jay-Jiguang Zhu,^j and Nicholas Butowski^k

Recurrent glioblastoma multiforme (GBM) is a highly aggressive cancer with poor prognosis, and an overall survival of 6 to 7 months with optimal therapies. The NovoTTF-100A™ System is a novel antimitotic cancer therapy recently approved for the treatment of recurrent GBM, based on phase III (EF-11) trial results. The Patient Registry Dataset (PRiDe) is a post-marketing registry of all recurrent GBM patients who received NovoTTF Therapy in a real-world, clinical practice setting in the United States between 2011 and 2013. Data were collected from all adult patients with recurrent GBM who began commercial NovoTTF Therapy in the United States between October 2011 and November 2013. All patients provided written consent before treatment was started. Overall survival (OS) curves were constructed for PRiDe using the Kaplan-Meier method. Median OS in PRiDe was compared for patients stratified by average daily compliance ($\geq 75\%$ v $< 75\%$ per day) and other prognostic variables. Adverse events were also evaluated. Data from 457 recurrent GBM patients who received NovoTTF Therapy in 91 US cancer centers were analyzed. More patients in PRiDe than the EF-11 trial received NovoTTF Therapy for first recurrence (33% v 9%) and had received prior bevacizumab therapy (55.1% v 19%). Median OS was significantly longer with NovoTTF Therapy in clinical practice (PRiDe data set) than in the EF-11 trial (9.6 v 6.6 months). One- and 2-year OS rates were more than double for NovoTTF Therapy patients in PRiDe than in the EF-11 trial (1-year: 44% v 20%; 2-year: 30% v 9%). First and second versus third and subsequent recurrences, high Karnofsky performance status (KPS), and no prior bevacizumab use were favorable prognostic factors. No unexpected adverse event was detected in PRiDe. As in the EF-11 trial, the most frequent

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Disclosures: The following authors received funding from Novocure clinical trial sponsorship: Herbert H. Engelhard, David Dinh Tran, Yvonne Kew, Robert Cavaliere, Daniela Annenelie Bota, Jeremy Rudnick, Ashley Love Sumrall, Jay-Jiguang Zhu, and Nicolas Butowski. Dr. Maciej Mrugala has received research funding from Novocure and has served on an advisory board sponsored by Novocure. Dr. John L. Villano, MD, PhD, has been a member of a speakers bureau and has served on an advisory board for Novocure.

Conflicts of interest: Advisory Board, Novocure; research funding: Novocure (EP-14 study).

This supplement was supported by Novocure, Inc., Haifa, Israel. Medical writing service and editorial support were provided by MDOL, Parsippany, NJ.

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0093-7754/-see front matter

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<http://dx.doi.org/10.1053/j.seminoncol.2014.09.010>

adverse events were mild to moderate skin reactions associated with application of the NovoTTF Therapy transducer arrays. Results from PRIDE, together with those previously reported in the EF-11 trial, indicate that NovoTTF Therapy offers clinical benefit to patients with recurrent GBM. NovoTTF Therapy has high patient tolerability and favorable safety profile in the real-world, clinical practice setting.

Semin Oncol ■■■■ © 2014 Published by Elsevier Inc.

Glioblastoma multiforme (GBM) is the most aggressive form of human glioma and accounts for approximately 60% to 70% of all malignant gliomas.^{1,2} Based on data from the 2013 Central Brain Tumor Registry of the United States (CBTRUS) statistical report on primary brain and CNS tumors in the United States, an estimated 9,600 to 11,200 new cases of GBM will be diagnosed in 2014.^{1,2} Virtually all patients with newly diagnosed GBM relapse despite maximal multimodality treatment,³ with a median time to recurrence of approximately 7 months.⁴ The prognosis for patients with recurrent GBM is even worse. The median progression-free survival (PFS) was only 9 weeks in the pre-bevacizumab era.⁵ In 2009, bevacizumab received accelerated approval from the US Food and Drug Administration (FDA) for the treatment for recurrent GBM based on two single-arm studies with favorable response rates and PFS data.^{1,6,7} Formal phase III data is not available in the recurrent setting, however phase III comparison of bevacizumab versus placebo in newly diagnosed glioblastoma patients failed to demonstrate prolongation of survival with bevacizumab.^{1,8} A major challenge in treatment of recurrent GBM, particularly with bevacizumab, is that the tumor eventually develops resistance to the drug. Moreover, bevacizumab-treated tumors may convert to a more aggressive phenotype histologically and exhibit infiltrative tumor growth as observed on magnetic resonance imaging (MRI).^{9,10} Furthermore, patients with recurrent GBM who progress following bevacizumab therapy are typically resistant to subsequent cytotoxic chemotherapies.^{1,11,12} Therefore, new treatments that can offer a different mechanism of action and potentially overcome resistance of GBM are desperately needed.

The NovoTTF-100A™ System (Novocure, Ltd., Haifa, Israel) is a novel antimitotic cancer therapy approved in 2011 by the US FDA for the treatment of recurrent supratentorial GBM,^{13,14} based on the results of a phase III trial comparing NovoTTF Therapy with best chemotherapy according to physician choice.¹⁵ The unique mechanism of action of NovoTTF Therapy involves localized delivery of alternating low-intensity, intermediate-frequency,

tumor-treating fields (TTFields) via non-invasive transducer arrays attached to the patient's scalp.¹⁴ In preclinical studies, TTFields have been shown to selectively kill or arrest the growth of rapidly dividing cancer cells including glioblastoma cell lines by disrupting both mitotic spindle formation and normal cytokinesis by interrupting cytoplasmic furrow formation.¹⁶⁻²⁰

The pivotal phase III (EF-11) trial that led to FDA approval of the device compared NovoTTF Therapy (n = 120) with best chemotherapy according to physician's choice (n = 117) in recurrent GBM patients from 28 institutions in seven countries.¹⁵ More than 80% of patients in the study had failed two or more prior chemotherapies, and 20% had experienced recurrence while on bevacizumab. Seventy-eight percent of the 116 patients who started NovoTTF Therapy completed at least one full-treatment course (4 weeks). The results demonstrated comparable median OS with NovoTTF Therapy compared with chemotherapy (6.6 v 6.0 months; hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.66 to 1.12; *P* = .27), together with fewer severe adverse events (6% v 16%, *P* = .022) and improved quality-of-life measures for the NovoTTF Therapy arm compared with chemotherapy. The most common adverse events with NovoTTF Therapy were mild to moderate skin irritation associated with the transducer arrays. Systemic adverse events commonly associated with chemotherapy were generally absent in patients receiving NovoTTF Therapy.

Given the mechanism of action of TTFields and the results of preclinical studies, optimal device compliance is required for therapeutic effectiveness with NovoTTF Therapy. NovoTTF Therapy does not have a half-life, therefore it requires continuous application to exert a therapeutic effect. This differs from systemic chemotherapy, which exerts anticancer effects between administrations due to the drug pharmacokinetics. Based on modeling of tumor growth kinetics and supporting preclinical and clinical data, NovoTTF Therapy must be administered almost "continuously" for at least 4 weeks in order to halt tumor growth and subsequently demonstrate an objective response.^{21,22} Recommended administration of NovoTTF Therapy

is ≥ 18 hours per day for each 4-week treatment cycle.²¹ A post hoc analysis of the phase III trial data recently showed significantly longer median OS in NovoTTF Therapy patients with a maximal monthly compliance rate $\geq 75\%$ (≥ 18 hours daily) versus those with a $< 75\%$ compliance rate (7.7 v 4.5 months, $P = .042$) (see Kanner in this supplement). A recent responder analysis also demonstrated very high compliance rates $> 90\%$ in EF-11 responders.²⁵

The Patient Registry DataSet (PRiDe) is a registry of 457 recurrent GBM patients who received NovoTTF Therapy in the clinical practice setting on the US commercial prescription-use program between October 2011 and November 2013. Patients treated in clinical trials often differ from those who receive treatment in the real-world setting due to patient selection criteria and frequently represent a less homogenous group. Hence registry data can be an important source of additional information about the efficacy and safety of a newly approved therapy. This report analyzes data from PRiDe to help us better understand the potential benefits of NovoTTF Therapy for patients with recurrent GBM, including analyses of median OS, tolerability, and the relationship between survival and compliance as well as other prognostic factors.

METHODS

Patients and Data Collection

PRiDe data were collected from all patients ≥ 18 years old with recurrent GBM who began commercial treatment with NovoTTF Therapy in the United States between October 2011 and November 2013. All participating patients provided written informed consent to use protected health information to advance the understanding of NovoTTF Therapy. Recurrent GBM was defined as histologically-confirmed, supratentorial GBM (World Health Organization grade IV astrocytoma) with radiologically confirmed evidence of disease progression, as defined by the Macdonald criteria,²⁴ following treatment with radiotherapy with or without concomitant and/or adjuvant chemotherapy. Patients who received NovoTTF Therapy were not restricted to the number or types of prior therapies or recurrences. Information about combination use of NovoTTF Therapy as part of the prescription-use program was not captured. Therefore some patients may have received combination therapy (chemotherapy or anti-vascular endothelial growth factor [VEGF] agents) rather than monotherapy.

Baseline characteristics were assessed by manual patient chart review. OS was collected using the Social Security Death Date Registry and obituaries. Novocure started collecting compliance data centrally

in January 2013, so such data are only available for under two thirds of patients in the registry. A monthly compliance assessment was performed for each patient by computer download of an internal log file which captures the cumulative amount of time therapy is delivered to the patient. Patient compliance was calculated as the average percentage of each day the system was delivering fields (out of each 24-hour period). In addition, other prognostic factors, such as the number of prior recurrences, age, KPS, prior bevacizumab use, and any debulking surgery were captured and analyzed. Adverse events were recorded prospectively according to National Cancer Institute Common Toxicity Criteria. Quality-of-life measures were not assessed in PRiDe.

Statistical Analysis

The OS and treatment duration curves were constructed using the Kaplan-Meier method. OS in PRiDe was compared to OS for patients receiving NovoTTF Therapy or best chemotherapy in the phase III EF-11 trial (ITT population) using a log-rank (Mantel-Cox) test. Patient or disease characteristics prognostic for survival with NovoTTF Therapy were assessed using a Cox proportional hazards model (P value of .15 for significant interactions). Subgroup analyses were performed on patient/clinical characteristics found to be significantly correlated with OS. A log-rank test was used to compare the relationship between OS and daily compliance ($< 75\%$ v $\geq 75\%$), prior debulking surgery (yes, no), KPS (90-100, 70-80, 10-60), recurrence number (1st, 2nd, 3rd-5th recurrence) and prior bevacizumab use (prior use v naïve).

RESULTS

Patient Characteristics

Four-hundred fifty-seven patients with recurrent GBM were treated with NovoTTF Therapy between October 2011 and November 2013 at 91 oncology centers. This population is more than three times the 120 subjects treated with NovoTTF monotherapy, as well as the 117 subjects treated with chemotherapy, in the phase III EF-11 trial, from which we were making a comparison. Baseline patient characteristics are presented in Table 1. Patient characteristics (age and gender) were generally similar in PRiDe and the two treatment groups in the EF-11 trial. Approximately one third of patients treated commercially with NovoTTF Therapy were women, which is an important observation given the perceived cosmetic considerations of head shaving and array placement.

Table 1. Baseline Patients and Clinical Characteristics for Patients With Recurrent Glioblastoma Multiforme in PRiDe and EF-11 Trial

| Characteristic | | PRiDe NovoTTF Therapy (n = 457) | EF-11 NovoTTF Therapy (n = 120) | EF-11 Chemotherapy (n = 117) |
|------------------|-------------------|---------------------------------|---------------------------------|------------------------------|
| Age (y) | Median (range) | 55 (18–86) | 54 (24–80) | 54 (29–74) |
| Gender | Male | 67.6% | 77% | 62% |
| | Female | 32.4% | 23% | 38% |
| KPS | Median (range) | 80 (10–100) | 80 (50–100) | 80 (50–100) |
| | 10–60 | 19.0% | NA | NA |
| | 70–80 | 46.6% | NA | NA |
| | 90–100 | 30.9% | NA | NA |
| Recurrence | Unknown | 3.5% | NA | NA |
| | Median (range) | 2 (1–5) | 2 (1–5) | 2 (1–4) |
| | First | 33.3% | 9% | 15% |
| | Second | 26.9% | 48% | 46% |
| Prior treatments | Third to Fifth | 27.4% | 43% | 39% |
| | Unknown | 12.5% | 0% | 0% |
| | Bevacizumab | 55.1% | 19% | 18% |
| | RT + temozolo- | 77.9% | 86% | 82% |
| | midle | | | |
| | Debulking surgery | 63.9% | 79% | 85% |
| | Carbustine wafers | 3.7% | NA | NA |

Abbreviations. KPS, Karnofsky performance status; NA, not applicable; RT, radiotherapy.

Tolerability and Safety

No new adverse events were detected in PRiDe compared to those found in EF-11. The most common device-related adverse events associated with NovoTTF Therapy in the registry were skin reactions/irritation and heat sensations on the scalp beneath the transducer arrays (Table 2). Patients sometimes described these events as "warmth" or "tingling" sensations, none of which were associated with injury to the patient. Systemic adverse events, which were often associated with chemotherapy (eg, gastrointestinal, hematologic, and infectious adverse events), were rare for patients treated with NovoTTF Therapy in the registry.

Survival Rates

Figure 1 presents Kaplan-Meier curves of OS for patients treated with NovoTTF Therapy in the clinical practice setting (PRiDe) and those who received NovoTTF Therapy or best chemotherapy as part of the EF-11 trial (ITT population). Median OS on NovoTTF Therapy appeared to be markedly longer in PRiDe than in the EF-11 trial (9.6 v 6.6 months). Median OS was also significantly longer with NovoTTF Therapy in PRiDe than with best chemotherapy group in the EF-11 trial (9.6 v 6.0 months). One- and 2-year OS rates for NovoTTF Therapy patients in PRiDe were more than double

those seen with either NovoTTF Therapy or best chemotherapy in the EF-11 trial (Table 3).

Median treatment duration for patients in PRiDe was 4.1 months (95% CI, 3.5–4.8). In comparison, the median treatment duration in the EF-11 study was 2.3 months (95% CI, 2.1–2.4) for NovoTTF Therapy arm and 2.1 months (95% CI, 2.0–2.9) for best chemotherapy. Figure 2 shows the fraction of NovoTTF Therapy patients still on treatment over time. Roughly 50% were still on NovoTTF Therapy after 4 months from treatment start, and roughly 10% were still on NovoTTF Therapy at 2 years after treatment start.

Compliance as a Prognostic Factor and Its Relationship to OS

Because of the major difference in the OS in patients registered in PRiDe as compared to the OS of subjects treated with NovoTTF monotherapy in EF-11, we sought to identify the prognostic factors in the former cohort. The first prognostic factor we analyzed was NovoTTF treatment compliance because it was found to be prognostically important in EF-11 in post hoc analysis. Compliance data was collected centrally starting in January 2013 and, therefore, were only available for 287 of the 457 patients (63%) in the registry. The median daily compliance was 70% for patients treated with NovoTTF Therapy in PRiDe (range, 12%–99%). One

Table 2. Adverse Events in Patients With Recurrent Glioblastoma Multiforme Treated With NovoTTF Therapy in PRiDe

| Adverse event | Percentage of Patients PRiDe (n = 457) |
|---------------------------|-------------------------------------------|
| Skin reaction | 24.3 |
| Heat sensation | 11.3 |
| Neurological disorder | 10.4 |
| Seizure | 8.9 |
| Electric sensation | 7.7 |
| Headache | 5.7 |
| Pain/discomfort | 4.7 |
| Fall | 3.9 |
| Psychiatric disorder | 2.9 |
| Gastrointestinal disorder | 2.9 |
| Fatigue | 2.5 |
| Vascular disorder | 1.6 |
| Weakness | 1.4 |
| Infections | 1.4 |
| Eye disorder | 1.3 |

hundred twenty-seven (44%) with available data achieved daily compliance of $\geq 75\%$ of each day, while 160 (56%) had daily compliance of $< 75\%$. As illustrated in Figure 3, median OS was significantly longer in patients with a NovoTTF Therapy daily compliance $\geq 75\%$ than in those with $< 75\%$ daily compliance (13.5 v 4.0%; HR, 0.43; 95% CI, 0.29–0.63; $P < .0001$).

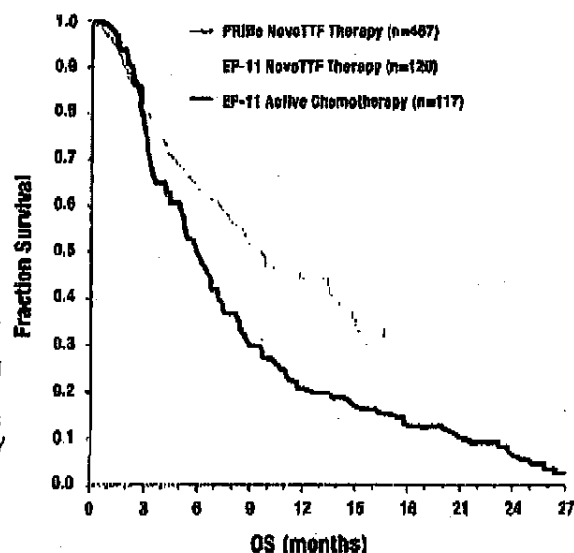


Figure 1. Kaplan-Meier overall survival (OS) curves for patients with recurrent glioblastoma multiforme treated with NovoTTF Therapy in PRiDe or with NovoTTF Therapy or best chemotherapy in the EF-11 trial.

Other Prognostic Factors

The Cox proportional hazards model identified the presence or absence of debulking surgery, number of prior recurrences, compliance, KPS, and prior bevacizumab therapy as significant independent predictors of OS in patients treated with NovoTTF Therapy in PRiDe ($P < .15$). Table 4 presents log-rank OS testing between patient subgroups in PRiDe for each of these prognostic factors; Figure 4 presents Kaplan-Meier survival curves for these same factors. First, no difference in median OS was observed between patients who did not have surgical debulking and those who did (8.9 v 9.8, respectively; HR, 1.1; 95% CI, 0.8–1.5; $P = .7927$). Second, recurrent GBM patients treated with NovoTTF Therapy in clinical practice at their first recurrence experienced a significantly longer median OS as compared to patients treated at their second, third, or subsequent recurrence (20 months compared to 8.5 and 4.9 months, respectively; HR, 0.6; 95% CI, 0.4–0.9; $p = 0.0271$ and HR, 0.3; 95% CI, 0.2–0.5; $P < .0001$). It should be noted that a greater percentage of patients in PRiDe were at their first GBM recurrence compared with patients treated with NovoTTF Therapy or best chemotherapy in the EF-11 trial (33.3% v 9% and 15%, respectively). In addition, differences were also apparent between patients in PRiDe and those in the EF-11 trial with respect to prior treatments. More than half of NovoTTF Therapy patients in PRiDe had previously received bevacizumab (55.1%), compared with only 19% of NovoTTF monotherapy and 18% of best active chemotherapy cohorts in the EF-11 trial. Third, recurrent GBM patients with KPS ≥ 90 experienced a near doubling of median OS compared with patients with a KPS of 70–80, median OS 14.8 versus 7.7 months, respectively, HR 0.6 (95% CI, 0.4–0.9), $P = .0070$. Lastly, the survival of bevacizumab-naïve patients was significantly longer compared to patients who had received prior bevacizumab before starting NovoTTF Therapy, with a respective median OS 13.4 versus 7.2 months, HR 0.5 (95% CI, 0.4–0.7), $P < .0001$. These data suggest

Table 3. One- and 2-Year Survival Rates for Patients With Recurrent Glioblastoma Multiforme Treated With NovoTTF Therapy in PRiDe and EF-11 trial, and With Best Chemotherapy in the EF-11 Trial

| Endpoint | PRiDe NovoTTF Therapy (n = 457) | EF-11 NovoTTF (n = 120) | EF-11 Chemo- (n = 117) |
|-----------------|------------------------------------------|-------------------------------|------------------------------|
| 1-Year survival | 44% | 20% | 20% |
| 2-Year survival | 30% | 9% | 7% |

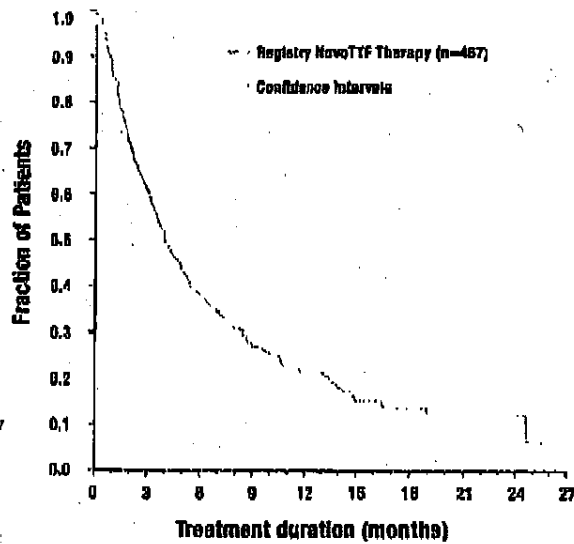


Figure 2. Fraction of NovoTTF Therapy patients alive by treatment duration (PRiDe).

that, within this heterogeneous group of patients registered in PRiDe, there were many patients who derived significant benefit from NovoTTF Therapy.

DISCUSSION

The Patient Registry Dataset, or PRiDe, represents 457 unselected patients with recurrent GBM who received NovoTTF Therapy in a real-world, clinical practice setting across 91 cancer centers in the United States between October 2011 and November 2013. No new, unexpected adverse event was detected with NovoTTF Therapy in this cohort. Similar to those found in the EF-11 trial,¹⁵ the most common adverse events associated with NovoTTF Therapy were mild to moderate skin reactions localized to the scalp beneath the transducer arrays. These reactions were easily treated with topical corticosteroids or antibiotics, were not associated with serious injury to the scalp, and typically did not require interruption of treatment. Some patients in PRiDe reported subjective sensations beneath the transducer arrays, often described as "warmth" or "tingling." These heat or electric sensations were captured as adverse events in PRiDe ("skin reaction"), but not in the EF-11 trial. These sensations occur when the contact between transducer arrays and the skin is suboptimal, and usually indicate the presence of hair regrowth. In these instances, re-shaving the head can re-establish optimal contact between the skin and transducer arrays. Furthermore, systemic adverse events commonly observed with chemotherapy were largely absent in patients

treated with NovoTTF Therapy in PRiDe as they were in the EF-11 trial.¹⁵

Patients receiving NovoTTF Therapy for recurrent GBM demonstrated a median OS of 9.6 months in clinical practice. This compares favorably to the reported median OS for the EF-11 pivotal trial cohort treated with NovoTTF monotherapy, where median OS was 6.6 months, and to OS of patients who received treatments for recurrent GBM in other clinical trials.²⁵⁻²⁹ For example, recent reports of median OS in recurrent GBM patients treated with bevacizumab are in the range of 6 to 10.5 months,^{7,12,25-27,29} and those treated with temozolomide in the range 6 to 9 months.³⁰⁻³² It should be noted that many of the longer term survivals noted in clinical trials of bevacizumab and temozolomide in recurrent GBM included small sample sizes and none were randomized.

The difference between the OS seen in clinical practice and in the EF-11 trial may in part be due to the greater percentage of patients with a first GBM recurrence in PRiDe versus patients in the EF-11 study (33.3% v 9%, respectively). This observation is also supported by a prior post hoc analysis of EF-11 that showed a significantly longer median OS in patients treated with NovoTTF Therapy at their first or second recurrence compared to those treated at third or subsequent recurrences. Furthermore, when used as intended (daily compliance $\geq 75\%$ or ≥ 18 hours daily), the median OS for patients treated with NovoTTF Therapy in PRiDe was remarkably high at 13.5 months compared to only 4.0 months in those who had suboptimal compliance (daily compliance $< 75\%$ or < 18 hours daily). Kanner et al (see accompanying Kanner article in this supplement)

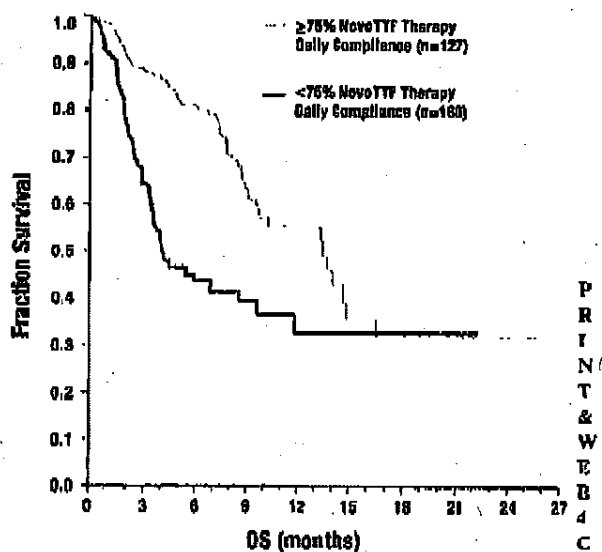


Figure 3.

PRiDe registry for glioblastoma patients receiving NovoTTF-100A

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Table 4. Results of Subgroup Analyses of Overall Survival (OS) in Patients With Recurrent Glioblastoma Multiforme Treated With NovoTTF Therapy in PRiDe Based on Prognostic Factors Significantly Correlated With OS in the Cox Proportional Hazards

| Variable | Median OS (mo) | Hazard Ratio | P Value |
|-------------------------------------------|----------------|-----------------------|---------------------|
| No. of recurrences | | | |
| 1st | 20 | — | — |
| 2nd | 8.5 | 0.6 (95% CI, 0.4–0.9) | .0271 ^a |
| 3rd–5th | 4.9 | 0.3 (95% CI, 0.2–0.5) | <.0001 ^b |
| Compliance | | | |
| ≥75% | 13.5 | 0.4 (95% CI, 0.3–0.6) | <.0001 |
| <75% | 4.0 | | |
| Karnofsky performance status (KPS) | | | |
| 90–100 | 14.8 | — | — |
| 70–90 | 7.7 | 0.6 (95% CI, 0.4–0.9) | .0070 ^c |
| 10–60 | 6.1 | 0.4 (95% CI, 0.2–0.6) | <.0001 ^d |
| Bevacizumab use | | | |
| Naïve | 13.4 | 0.5 (95% CI, 0.4–0.7) | <.0001 |
| Prior use | 7.2 | | |
| Debulking surgery | | | |
| No | 8.9 | 1.1 (95% CI, 0.8–1.5) | .7927 |
| Yes (any surgery) | 9.8 | | |

^a First recurrence compared to 2nd recurrence.^b First recurrence compared to 3rd–5th recurrence.^c KPS 90–100 compared to KPS 70–80.^d KPS 90–100 compared to KPS 10–60.

recently reported similar findings when re-examining data from the EF-11 trial: median OS was significantly longer with a monthly compliance rate for NovoTTF Therapy ≥75% than <75% (7.7 v 4.5 months, $P = .042$). The compliance findings from each of these studies are consistent with the mechanism of action of NovoTTF Therapy, which depends on almost continuous administration (≥18 hours per day) for a prolonged period of time (≥4 weeks).^{21,22} However, patients in PRiDe who had suboptimal compliance were also found to have lower KPS and were, in general, at later stages of their disease. It is unclear whether they also may have had larger tumors or inadequate social support. Nevertheless, consistent with previous findings, our data suggest that applying NovoTTF Therapy to patients with higher performance status, earlier in their recurrence and ensuring treatment compliance, can maximize clinical benefit.

Additional analyses uncovered other prognostic factors that were important for patients in PRiDe. Of interest, in our subgroup analysis, 55.1% of patients in PRiDe who received prior bevacizumab therapy demonstrated a shorter median OS of 7.2 months, as compared to a median OS of 13.4 months in bevacizumab-naïve patients. The shorter survival in patients treated previously with bevacizumab may be a result of acquired tumor resistance and development of a more aggressive phenotype with infiltrative tumor progression on MRI.^{9,10} Moreover,

patients with recurrent GBM tumors that progress while on bevacizumab therapy are typically resistant or refractory to subsequent cytotoxic chemotherapy,^{1,11,12} and have a median OS of just 2.7 months. Therefore, the PRiDe data suggest that at least a percentage of bevacizumab-resistant tumors remain responsive to NovoTTF Therapy. Future analysis of responders and nonresponders to NovoTTF Therapy will need to include molecular genetic analysis of the tumor (and especially MGMT methylation status), the estimated tumor size (volume) as measured by fluid attenuated inversion recovery sequence on MRI, and more detailed analysis of the extent of resection.

Our analysis of KPS in PRiDe also demonstrated that higher KPS correlated with longer OS. It is unclear at this time whether or not patients who had KPS 90–100 had smaller tumors than the rest of the cohort or perhaps more extensive resections. KPS is often, but not always, a measure of tumor size, particularly the microscopic invasive component of the glioblastoma. Whether or not the median tumor size, as measured by gadolinium-enhanced T1-weighted and/or FLAIR MRI, differ between the subgroup with KPS 90–100 versus 70–90 and 10–60 remains to be determined. Of note, age was not a predictor of OS in the PRiDe dataset when evaluated either by direct correlation (Pearson correlation coefficient) or a Cox proportional hazards model ($P = .20$). In addition, age was

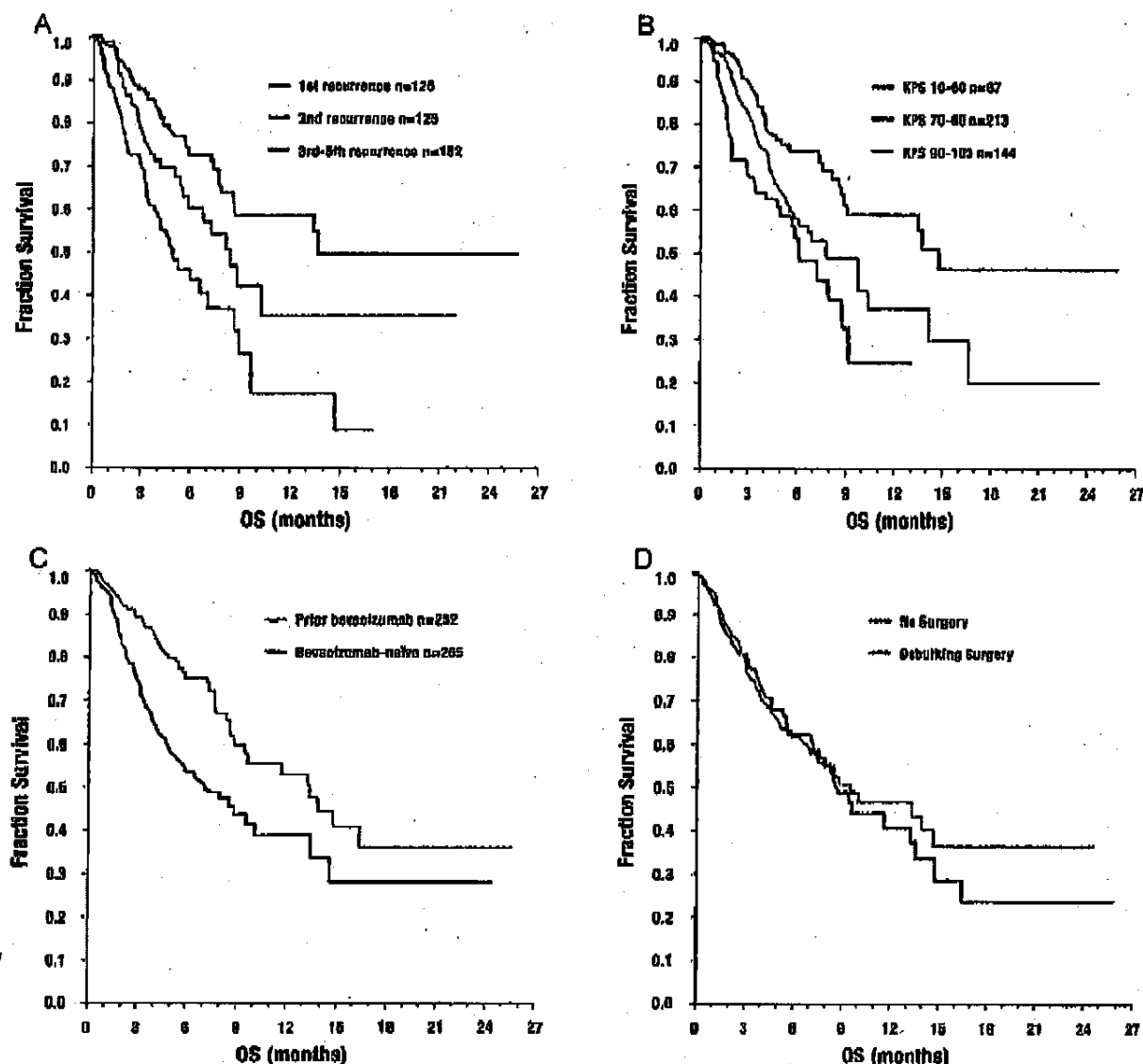


Figure 4. Kaplan-Meier overall survival (OS) curves for recurrent glioblastoma multiforme patients treated with NovoTTF Therapy in PRiDe based on (A) recurrence number, (B) Karnofsky performance status (KPS), (C) prior bevacizumab use, and (D) prior debulking surgery, respectively.

not correlated with compliance in the PRiDe (correlation coefficient = 0.02; $P = .37$). Taken in the context of the overall efficacy results, these findings suggest NovoTTF Therapy works well for patients of all ages and that advanced age is not associated with lower compliance. It would also be interesting to know if marital status (or other measures of patient support) influence compliance and survival, but data on marital status were not collected in PRiDe.

Finally, the PRiDe dataset did not capture patients on combination treatments in which additional biologic therapy or chemotherapy were added to

NovoTTF Therapy in a combined regimen. It is possible that the longer survival seen in clinical practice with NovoTTF Therapy compared to NovoTTF monotherapy in the EF-11 trial is a reflection of combination use of NovoTTF Therapy with biological agents or cytotoxic chemotherapy. In fact, preclinical data have suggested that TTFs are additive or even synergistic with chemotherapies in cell culture.³³⁻³⁵ Therefore, the potential benefits of combining NovoTTF Therapy with other systemic therapies warrant further investigation. A phase III trial of NovoTTF Therapy together with temozolomide compared to temozolomide alone is currently

ongoing in patients with newly diagnosed glioblastoma. The results of this trial will shed light on the possible additive effects of NovoTTF Therapy and systemic chemotherapy.

In summary, PRiDe and the EF-11 trial represent one of the largest datasets of patients with recurrent GBM published to date, containing 700 patients in total, 567 of whom were treated with NovoTTF Therapy. The results, individually and collectively, provide further support for the use of NovoTTF Therapy to treat recurrent, supratentorial GBM. Observations from the post-marketing registry demonstrate that the safety and efficacy observed with NovoTTF Therapy in a clinical trial extend to the real-world, clinical practice setting. Future investigations may need to include NovoTTF Therapy in combination with other recurrent GBM treatments, which together may have additive or synergistic effects on patient outcome.

Acknowledgments

The final manuscript was written by Maciej M. Mrugala with substantive input from all the coauthors, and with logistical and editorial assistance from MDOL, Inc.

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Curr. Treat. Options in Oncol. (2015) 16:40
DOI 10.1007/s11864-015-0353-5

Neuro-oncology (C. J. Lesser, Section Editor)

An Evidence-Based Review of Alternating Electric Fields Therapy for Malignant Gliomas

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This article is part of the Topical Collection on *Neuro-oncology*

Keywords Alternating electric fields • Malignant gliomas • Glioblastoma • Review

Opinion statement

Glioblastoma is a deadly disease and even aggressive neurosurgical resection followed by radiation and chemotherapy only extends patient survival to a median of 1.5 years. The challenge in treating this type of tumor stems from the rapid proliferation of the malignant glioma cells, the diffuse infiltrative nature of the disease, multiple activated signal transduction pathways within the tumor, development of resistant clones during treatment, the blood brain barrier that limits the delivery of drugs into the central nervous system, and the sensitivity of the brain to treatment effect. Therefore, new therapies that possess a unique mechanism of action are needed to treat this tumor. Recently, alternating electric fields, also known as tumor treating fields (TTFields), have been developed for the treatment of glioblastoma. TTFields use electromagnetic energy at an intermediate frequency of 200 kHz as a locoregional intervention and act to disrupt tumor cells as they undergo mitosis. In a phase III clinical trial for recurrent glioblastoma, TTFields were shown to have equivalent efficacy when compared to conventional chemotherapies, while lacking the typical side effects associated with chemotherapies. Furthermore, an interim analysis of a recent clinical trial in the upfront setting demonstrated superiority to standard of care cytotoxic chemotherapy, most likely because the subjects' tumors were at an earlier stage of clonal evolution, possessed less tumor-induced immunosuppression, or both. Therefore, it is likely that the efficacy of TTFields can be increased by combining it with other anti-cancer treatment modalities.

Published online: 05 July 2015

Introduction

Tumor treating fields (TTFields) represent a novel treatment modality for cancer that utilizes alternating electric fields at an intermediate frequency of 200 kHz. At this specific frequency, TTFields have been shown to penetrate into the head from the surface of the scalp. Computational modeling also showed that the fields are distributed inhomogeneously within the supratentorial regions of the brain, and they tend to become intensified near the ventricles [1•]. At the cellular level, the electromagnetic energy perturbs proteins that have large dipole moments. Cells treated with TTFields exhibited a variety of abnormalities indicative of mitotic catastrophe and aberrant mitotic exit, including cells in polyploidy prophase, rosettes, multi-spindled metaphase, single-spindled metaphase, and asymmetric anaphase [2]. Indeed, cells exhibit violent membrane blebbing as they enter anaphase and attempt to divide. This results in aberrant mitotic exit and subsequent cell death [3••]. Some of the proteins that are critical for the proper progression through mitosis have sufficiently high dipole moments to suggest that they may be targets of TTFields, including the mitotic septin complex and the α/β -tubulin monomeric subunit of tubulin. Septins constitute a family of GTP-binding proteins and septin 2, 6, and 7 oligomerize into a heterotrimer with an extremely large dipole moment of 2711 Debyes [4]. Importantly, this septin complex is required for functions that are necessary for the later stages of cell division. Septin 2, 6, and 7 heterotrimers rapidly polymerize and structurally organize within the cytokinetic furrow as cells exit metaphase.

Once it is recruited, it then organizes contractile elements within the cytokinetic furrow above the equatorial cleavage plane by binding to F-actin filaments and spatially regulates myosin activation. RNAi-directed depletion of septin subunits of the heterotrimer results in mitotic catastrophe similar to that seen when cells attempt to divide in the presence of TTFields [5]. We have shown that TTFields disrupt the ability of septins to re-localize to the cytokinetic furrow and reduce the accumulation of F-actin [3••]. Therefore, TTFields affect tumor cells by interfering with their ability to complete mitosis by exerting electromagnetic induction forces that interfere with the function of proteins with high dipole moments [2, 3••].

TTFields therapy has been shown to have equivalent efficacy when compared to the best physician's choice chemotherapy in a registration phase III clinical trial for recurrent glioblastoma [6]. This led to the FDA approval on April 8, 2011 for recurrent glioblastoma [Http://Www.Accessdata.Fda.Gov/Cdrh_Docs/Pdf/10/P100034a.Pdf]. Interim analysis of the most recent phase III study in the newly diagnosed setting showed a significant improvement of outcomes leading to a crossover of subjects from the control arm to the experimental arm of the trial [7]. Here, we review our current understanding of the mechanisms of TTFields therapy, particularly from the physics and cell biology perspectives, as well as the available clinical data when it is applied to the treatment of glioblastoma.

Electric field distribution within the brain

At a frequency of 200 kHz, the electric fields from the surface of the scalp can permeate into the brain. This is because the penetration of electromagnetic waves through any medium is frequency dependent. Past analyses have shown that the permittivity values were similar among the calvarial bone, gray matter, and white matter, while the conductivity values varied somewhat among these three structures [8].

The electric field intensity was directly measured in a patient receiving TTFields therapy while undergoing surgery for obstructive hydrocephalus from a large pineal meningioma at the Rambam Medical Center in Haifa, Israel. The measured intensity of electric field was validated to within 10 % of the simulated value using finite element method simulation [9].

Using finite element analysis, 3-dimensional mapping of the electric field distribution within the brain revealed inhomogeneous distribution of the fields, with a higher field strength near the ventricular horns that is most likely a result of the high conductivity of the cerebrospinal fluid (Fig. 1).

Cell biology effects of alternating electric fields on dividing tumor cells

TTFields disrupt the mitotic process in dividing tumor cells that results in violent membrane blebbing [3••, 10]. This results in the disordering of chromosomes from the metaphase plate during late metaphase or early anaphase, followed by aberrant mitotic exit in the absence of cytokinesis resulting in multinucleated cells and subsequent apoptosis [3••].

The septin 2, 6, and 7 family members heterotrimerize into a protein complex that possesses an extremely large dipole moment of 2711 Debyes, and it is active in mitosis [4]. This complex serves to regulate contractile function within the cytokinetic furrow, and it is likely to provide tensile strength needed within the submembranous cortical cytoskeleton to restrain the hydrostatic pressures within the cytoplasm during cell division. It has been shown to be a target of alternating electric fields, and the disruption of this protein results in disordered segregation of chromosome and cytoplasmic contents [3••].

Following TTFields-induced aberrant mitotic exit, cells exhibit signs of cellular stress that mark them for immune destruction and facilitate immune activation. Specifically, this type of cellular stress causes increased cell surface expression of the endoplasmic reticulum chaperonin calreticulin and the secretion of HMGB1 that acts as a danger signal when released from cells [11]. The presence of calreticulin on the plasma membrane is also seen in virally infected cells, as well as tumor cells exposed to certain chemotherapy agents [12]. This has been termed "immunogenic cell death" to differentiate it from apoptosis, which is immunosuppressive. Immunogenic cell death leads to tumor destruction.

There is a compelling evidence that TTFields increase the anti-tumor immunogenicity in vivo. When highly metastatic VX-2 tumors were injected into the kidney capsule of rabbits and treated with TTFields for 7 days then allowed to grow for an additional 21 days, the number of pulmonary metastases was significantly reduced when compared to untreated control animals [13]. When the lung metastases were recovered from animals, there was increased infiltration of immune cells in the TTFields-treated metastases as compared with the non-treated ones [14].

Treatment

The management of malignant gliomas should be undertaken in a multimodal fashion, with neurosurgical input, radiation oncology expertise, and chemotherapy administration. Now, with the availability of alternating electric fields therapy as a fourth modality of treatment, neuro-oncologists will need to factor in this therapy within the spectrum of available treatments. For newly diagnosed malignant gliomas, maximal safe neurosurgical resection is still

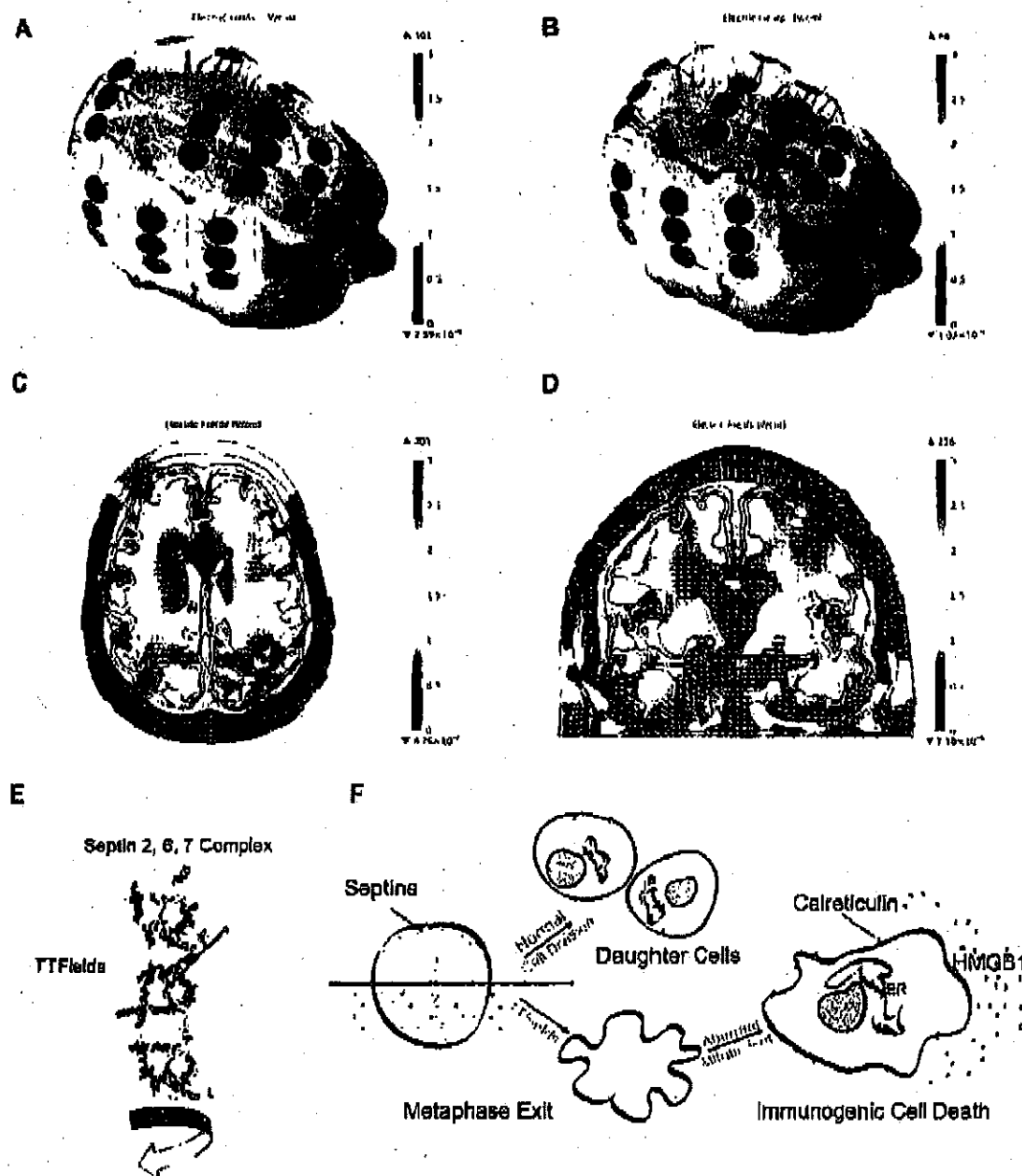


Fig. 1. A 3-dimensional render of a human head with TTFields clinically applied via electrode arrays on a glioblastoma patient whose gross tumor volume is on the right side. a Streamlines showing the magnitude of the electric field and direction of the current emanating from each electrode on the surface of the scalp. b Red arrows indicating vector field of the electric field distribution inside the brain. The intracranial electric fields are displayed in c axial and d coronal planes. e TTFields induce a force on the septin 2, 6, and 7 complex that has an extremely large dipole moment of 2711 Debyes. f This results in mitotic catastrophe and aberrant mitotic exit, leading to an increased cell surface expression of the endoplasmic reticulum chaperonin calreticulin and the secretion of HMGB1 that acts as a danger signal when release from cells, both of which are essential for immunogenic cell death.

recommended and resection accomplishes two goals of establishing a histological diagnosis and achieving cytoreduction. Although it has not been subjected to a randomized clinical trial, the best evidence for a benefit of cytoreduction is based on a retrospective analysis showing a 4.2-month survival advantage in patients with at least a 98 % resection versus those with less than 98 % [15]. However, if safe resection is not possible, biopsy to obtain a histological diagnosis is still indicated. Once a diagnosis of glioblastoma is established, patients proceed to standard of care treatment, which consists of external beam, involved-field cranial radiotherapy plus concomitant daily temozolomide, followed by 6 cycles of adjuvant temozolomide [16]. Alternatively, patients may be enrolled in a clinical trial at initial diagnosis and, depending on the conduct of the trial, may either receive treatment independently or in conjunction with standard of care treatment. Although upfront treatment can provide a period of stabilization for the glioblastoma, recurrence is the rule and additional treatments are typically needed to control tumor progression, alleviate neurological deficits, or both.

At the time of tumor recurrence, patients with a Karnofsky performance score of 70 or higher may be eligible for clinical trials. Those who are ineligible can be treated with single-agent bevacizumab or TTFields therapy since both were approved by the FDA for recurrent glioblastoma in 2009 and 2011, respectively. The benefit of bevacizumab was based on two single-arm phase II studies demonstrating a radiographic response rate of 30–40 % [17, 18]. However, infiltrative glioblastoma is the typical pattern of relapse and salvage chemotherapy after bevacizumab failure only offered a median overall survival of 5.2 months and progression-free survival of 2.0 months [19]. Therefore, alternative treatments are desperately needed for this population and TTFields therapy was demonstrated to have equivalent efficacy when compared to chemotherapy in this setting [6]. However, the optimal use of this device and its combination with conventional treatments are awaiting further investigation. Here, we review the currently available clinical data when it is applied to the treatment of glioblastoma, which is also summarized in Table 1.

TTFields therapy for recurrent glioblastoma

At present, the only indication approved by the FDA is for the treatment of recurrent glioblastoma. This is based on the registration phase III clinical trial (ClinicalTrials.gov: NCT00379470) demonstrating equivalent efficacy between TTFields therapy and best physician's choice chemotherapy (based on the best available treatment as offered by the treating physician) [6].

The primary endpoint of the trial was overall survival, and the median overall survival was 6.6 months for TTFields ($n=120$) versus 6.0 months for the best physician's choice chemotherapy ($n=117$), with a hazard ratio of 0.86 (95 % CI 0.66–1.12; $P=0.27$). It is notable that 31 % of the BPC cohort received bevacizumab alone or in combination with chemotherapy. The median progression-free survival of TTFields and the best physician's choice chemotherapy was 2.2 and 2.1 months, respectively, with a hazard ratio of 0.81 (95 % CI 0.60–1.09; $P=0.16$), and the progression-free survival at 6 months was 21.4 % (95 % CI 13.5–29.3) and 15.1 % (95 % CI 7.8–22.3), respectively ($P=0.13$). One year survival rate was 20 % in both cohorts.

Table 1. Summary of clinical data on TTFIELDS treatment for malignant gliomas

| Phase III trial for newly diagnosed glioblastoma interim analysis | TTFIELDS treatment + temozolomide | Temozolomide alone | Hazard ratio | P |
|-------------------------------------------------------------------|-----------------------------------|----------------------------------|--------------------------|-------|
| Overall survival, median ^a | 19.6 months | 16.6 months | 0.75 | 0.03 |
| Progression-free survival ^a | 7.1 months | 4.0 months | 0.63 | <0.01 |
| Phase III recurrent glioblastoma | | Active chemotherapy (n=117) | | |
| Overall survival, median ^b | 6.6 months | 6.0 months | 0.86 (95 % CI 0.66–1.12) | 0.27 |
| 1-year survival | 20 % | 20 % | | |
| 2-year survival | 8 % | 4 % | | |
| 3-year survival | 5 % | 1 % | | |
| Prognostic factors, median overall survival ^c | | | | |
| Prior bevacizumab failure | 6.0 months (n=23) | 3.3 months (n=21) | 0.43 (95 % CI 0.22–0.85) | 0.02 |
| Prior low-grade glioma | 25.3 months (n=12) | 7.7 months (n=9) | 0.31 (95 % CI 0.09–0.99) | 0.05 |
| Tumor size ≥18 cm ³ | 5.6 months (n=39) | 3.3 months (n=41) | 0.53 (95 % CI 0.32–0.85) | <0.01 |
| Karnofsky performance status ≥80 | 7.9 months (n=83) | 6.1 months (n=77) | 0.71 (95 % CI 0.51–0.98) | 0.05 |
| TTFIELDS treatment versus bevacizumab | 6.6 months (n=120) | 4.9 months (n=36) | 0.64 (95 % CI 0.41–0.99) | 0.05 |
| Progression-free survival, median ^b | 2.2 months | 2.3 months | 0.81 (95 % CI 0.60–1.09) | 0.13 |
| PFS at 6 months | 21 % | 15 % | | |
| Responders ^a | 14 | 7 | | |
| Response status, median overall survival | | | | |
| Partial and complete response versus stable disease | 24.7 months (n=14) | | | |
| Progressive disease | 7.6 months (n=34) | | | |
| Prognostic factor in TTFIELDS treatment responders ^d | 5.5 months (n=59) | | | |
| Overall survival, median | | | | |
| With prior low-grade glioma | 27.7 months | | | |
| Without prior low-grade glioma | 16.6 months | | | |
| Daily dexamethasone dose, median | | | | |
| Responders | 1.0 mg | | | |
| Nonresponders | 5.2 mg | | | |
| Cumulative dexamethasone dose, median | | | | |
| Responders | 7.1 mg | | | |
| Nonresponders | 261.7 mg | | | |
| Treatment-related adverse events, grade ≥3 ^{e,f} | | | | |
| Hematological | 3 % | 17 % | | |
| Gastrointestinal | 4 % | 17 % | | |
| Dermatological | 2 % | 0 % | | |
| Nervous system disorders | 30 % | 28 % | | |
| Recurrent glioblastoma from patient registry data set (PREDa) | PRIDE TTFIELDS treatment (n=457) | EF-13 TTFIELDS treatment (n=120) | | |
| Survival ^g | | | | |
| 1-year survival | 44 % | 20 % | | |
| 2-year survival | 30 % | 9 % | | |

Table 1. (Continued)

| Phase III trial for newly diagnosed glioblastoma interim analysis | Fields treatment + temozolomide | Temozolomide alone | Hazard ratio | P |
|-------------------------------------------------------------------|---------------------------------|--------------------|--------------|---|
| Prognostic factors, median overall survival ^a | | | | |
| Number of prior recurrences | 20 months | | | |
| First recurrence versus | 8.5 months, HR=0.6 | | | |
| Second recurrence | (95 % CI 0.4–0.9), P=0.03 | | | |
| Third to fifth recurrence | 4.9 months, HR=0.3 | | | |
| | (95 % CI 0.2–0.5), P<0.01 | | | |
| Compliance | 4.0 months | | | |
| <75 % versus | 13.5 months, HR=0.4 | | | |
| ≥75 % | (95 % CI 0.3–0.6), P<0.01 | | | |
| Karnofsky performance status | 14.8 months | | | |
| 90–100 versus | 7.7 months, HR=0.6 | | | |
| 70–90 | (95 % CI 0.4–0.9), P<0.01 | | | |
| 10–60 | 6.1 months, HR=0.4 | | | |
| | (95 % CI 0.2–0.6), P<0.01 | | | |
| Prior bevacizumab use | 13.4 months | | | |
| No versus | 7.2 months, HR=0.5 | | | |
| Yes | (95 % CI 0.4–0.7), P<0.01 | | | |
| Prior debulking surgery | 8.9 months | | | |
| No versus | 9.8 months, HR=1.1 | | | |
| Yes | (95 % CI 0.8–1.5), P=0.79 | | | |

^aSupp R, Wong ET, Scott C, et al. Neuro-Oncol 2014;16(Suppl 5):167^bSupp R, Wong ET, Kanner AA, et al. Eur J Cancer 2012;48:2192–2202^cKanner AA, Wong ET, Villano JL, et al. Semin Oncol 2014;41(Suppl 6):S25–S34^dAyoubzai J, Wong ET. Semin Oncol 2014;41(Suppl 6):S14–S24^eWong ET, Lok E, Swanson KD, et al. Cancer Med 2014;3:592–602^fLacouture ME, Davis ME, Eztinger G, et al. Semin Oncol 2014;41(Suppl 4):S1–S14^gMugala MH, Engelhard HH, Tran DD, et al. Semin Oncol 2014;41(Suppl 6):S4–S13

The most common toxicity associated with the device was grade 1 or 2 scalp irritation at a rate of 16 %, but none had severity of grade 3 or 4. The scalp irritation can be managed by applying topical corticosteroid and by shifting of the arrays slightly during each array exchange [20]. The most important advantage associated with the TFields therapy device, when compared to chemotherapy, is that it has far fewer grade 2 or greater hematological toxicities, 3 versus 17 %, respectively, and fewer adverse gastrointestinal events, 4 versus 17 %, respectively.

Analysis of quality of life demonstrated that patient treated with the device had better cognitive and emotional functions than those treated with chemotherapy while appetite loss, constipation, diarrhea, fatigue, nausea, vomiting, and pain were more often seen in patients treated with chemotherapy. Based on the equivalent efficacy results and the lack of serious toxicities, the TFields therapy device was approved by US FDA on April 8, 2011 for the treatment of recurrent glioblastoma.

Post hoc analysis showed that a higher proportion of responders had secondary glioblastoma than nonresponders [21••]. Five of the 14 responders (36 %) treated with TFields monotherapy had prior low-grade histology while none of the seven responders (0 %) treated with the best physician's choice chemotherapy did.

The analysis also showed that responders used less dexamethasone than nonresponders [21••]. In the TFields therapy cohort, the median daily dexamethasone dose used was 1.0 mg for responders versus 5.2 mg for nonresponders ($P=0.0019$) and the median cumulative dexamethasone dose was 7.1 mg for responders versus 261.7 mg for nonresponders ($P<0.0001$). In the best physician's choice chemotherapy cohort, the median daily dexamethasone dose used was 1.2 mg for responders versus 6.0 mg for nonresponders ($P=0.0041$) and the median cumulative dexamethasone dose was 348.5 mg for responders versus 242.3 mg for nonresponders ($P=0.9520$). These data suggest that concurrent dexamethasone use may influence the efficacy of TFields therapy.

TFields therapy as used in clinical practice

Patients who received treatment from the TFields device in clinical practice may have different clinical characteristics and outcomes from those who participated in the registration trial. To determine whether or not this is the case, a patient registry dataset (PRiDe) was developed in an effort to capture clinical practice data pertaining to the use of TFields therapy. At the time of publication, this dataset included 457 patients from 91 treatment centers in the USA [22•].

The median OS was 9.6 months among patients treated in PRiDe as compared to 6.6 months in the TFields monotherapy arm in the phase III trial while the 1-year OS rate was also longer at 44 % as compared to 20 %, respectively [6, 22•]. It is important to note that some patients in PRiDe may have used other treatments, such as conventional cytotoxic chemotherapy, bevacizumab, or even alternative medicine, in conjunction with TFields therapy, but this aspect of treatment was not adequately captured because this dataset is from a registry.

About 33 % of patients at their first glioblastoma recurrence used TFields therapy as compared to only 9 % in the registration phase III clinical trial [22•].

Favorable prognostic factors for patient survival include treatment with TTFields therapy at first or second relapses versus third or later recurrences, as well as no prior bevacizumab use [22*].

TTFields therapy for newly diagnosed glioblastoma

TTFields therapy is currently being tested in a randomized phase III clinical trial for subjects with newly diagnosed glioblastoma (NCT0915409). The goal of this study is to compare the efficacy of TTFields plus adjuvant temozolomide versus adjuvant temozolomide alone by randomizing the subjects to the respective treatment arms in a 2:1 fashion, after the completion of initial treatment with radiation and concomitant daily temozolomide [16]. The primary endpoint is progression-free survival, and the secondary endpoints are overall survival, progression-free survival at 6 months, survival at 1 and 2 years, as well as quality of life assessment. So far, all 700 pre-specified subjects have been enrolled and randomized.

In a pre-specified interim analysis of the first 315 subjects after a minimum follow-up of 18 months, the intent-to-treat cohort received TTFields plus temozolomide ($n=210$) had a longer progression-free survival than the cohort treated with temozolomide alone ($n=105$), median 7.1 (95 % CI 5.9–8.2) months versus 4.0 (95 % CI 3.0–4.3) months (HR=0.63, Log rank $P=0.0014$). The median overall survival also favors the TTFields plus temozolomide group, 19.6 (95 % CI 16.5–24.1) months versus 16.6 (95 % CI 13.5–19.1) months, respectively (HR=0.75, Log rank $P=0.034$), as well as the per protocol population that started the second cycle of treatment, 20.5 (95 % CI 16.5–24.1) months ($n=196$) versus 15.5 (95 % CI 13.5–19.1) months ($n=84$), respectively (HR=0.67, Log rank $P=0.0042$).

There were no unexpected adverse events between the TTFields plus temozolomide and the temozolomide alone cohorts, and respective grade 3 and 4 hematological toxicities (12 versus 9 %), gastrointestinal disorders (5 versus 2 %), and convulsions (7 versus 7 %) were similar. Scalp reaction, however, was more common in the device-treated cohort, 49 % for grades 1 and 2 as well as 7 % for grade 3 and 4 toxicities, than the temozolomide-only cohort, 5 % for grade 1 and 2 toxicities as well as 5 % for grade 3 and 4 toxicities.

The follow-up of the remaining trial subjects will most likely mature in another year such that final data from the trial will be available by the end of 2016.

Additional investigational studies of TTFields therapy for the central nervous system or other malignancies

Combinations with TTFields are being studied in patients with recurrent glioblastoma including bevacizumab (NCT01894061) and bevacizumab together with hypofractionated stereotactic irradiation (NCT01925573).

TTFields therapy is currently being investigated in patients with other types of central nervous system malignancies, including its use for recurrent atypical and anaplastic meningiomas (NCT01892397), as well as in those patients with 1–5 brain metastases from non-small cell lung cancer (NCT01755624).

TFields therapy is also being investigated in systemic malignancies, including its use in combination with gemcitabine for advanced pancreatic adenocarcinoma (NCT01971281), in combination with paclitaxel in recurrent ovarian carcinoma (NCT02244502), as well as in combination with pemetrexed and cisplatin or carboplatin for malignant pleural mesothelioma (NCT02397928).

Compliance with Ethics Guidelines

Conflict of Interest

Eric T Wong received an unrestricted grant from Novocure for the investigation of the cell biology effects of TFields; participated in the registration trial for recurrent glioblastoma and the PRiDe dataset; and has received sponsored clinical research through grants from AngioChem, AstraZeneca, Cephalon, Eli Lilly, Northwest Biotherapeutics, Novartis, Pfizer, and Plexxikon.

Edwin Lok declares that he has no conflict of interest.

Kenneth D. Swanson received an unrestricted grant from Novocure for the investigation of the cell biology effects of TFields and has also received a reimbursement for travel expenses for training on use of laboratory equipment and an honorarium for a lecture at Novocure headquarters to present the results of basic research studies.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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BJC

FULL PAPER

Keywords: dexamethasone; glioblastoma; NovoTTF-100A; tumour immunology; chemotherapy

Dexamethasone exerts profound immunologic interference on treatment efficacy for recurrent glioblastoma

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Background: Patients with recurrent glioblastoma have a poor outcome. Data from the phase III registration trial comparing tumour-treating alternating electric fields (TTFields) vs chemotherapy provided a unique opportunity to study dexamethasone effects on patient outcome unencumbered by the confounding immune and myeloablative side effects of chemotherapy.

Methods: Using an unsupervised binary partitioning algorithm, we segregated both cohorts of the trial based on the dexamethasone dose that yielded the greatest statistical difference in overall survival (OS). The results were validated in a separate cohort treated in a single institution with TTFields and their T lymphocytes were correlated with OS.

Results: Patients who used dexamethasone doses >4.1 mg per day had a significant reduction in OS when compared with those who used ≤ 4.1 mg per day, 4.8 vs 11.0 months respectively ($\chi^2 = 34.6$, $P < 0.0001$) in the TTField-treated cohort and 6.0 vs 8.9 months respectively ($\chi^2 = 10.0$, $P < 0.0015$) in the chemotherapy-treated cohort. In a single institution validation cohort treated with TTFields, the median OS of patients who used dexamethasone >4.1 mg per day was 3.2 months compared with those who used ≤ 4.1 mg per day was 8.7 months ($\chi^2 = 11.1$, $P = 0.0009$). There was a significant correlation between OS and T-lymphocyte counts.

Conclusions: Dexamethasone exerted profound effects on both TTFields and chemotherapy efficacy resulting in lower patient OS. Therefore, global immunosuppression by dexamethasone likely interferes with immune functions that are necessary for the treatment of glioblastoma.

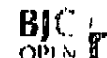
Patients with recurrent glioblastoma have limited treatment options. Bevacizumab is a standard of care for patients with recurrent glioblastoma and it produces an objective response rate of 25–60% (Wong *et al.* 2011). However, its ability to prolong patient overall survival (OS) is questionable (Iwamoto and Fine, 2010; Reardon *et al.* 2012). The NovoTTF-100A device is another FDA-approved treatment for recurrent glioblastoma that works by emitting tumour-treating alternating electric fields (TTFields) via two pairs of transducer arrays placed orthogonally on the scalp and acts to perturb tumour cells during mitosis (Kliron *et al.* 2004, 2007; Gera *et al.* 2015). Preclinical data show that cells affected by TTFields exhibit violent plasma membrane blebbing that disrupts the normal spatial ordering of the mitotic chromosomes.

This results in asymmetric chromosome segregation and aneuploidy owing to defects in cytokinesis and aberrant mitotic exit. Furthermore, these cells also exhibit signs of stress that include elevated cell surface expression of calreticulin, which makes them more readily detectable by phagocytic immune cells, facilitating an immune response against the tumour (Lee *et al.* 2013). Importantly, the NovoTTF-100A device was demonstrated to possess equivalent efficacy when compared with best physician's choice (BPC) chemotherapy in the registration phase III clinical trial, but without the myeloablative toxicities associated with systemic chemotherapies that may cause secondary systemic infection or interference with immune effector function (Vecht *et al.* 1994; Hughes *et al.* 2005; Stupp *et al.* 2012; Fonken and Wong, 2012).

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Revised 23 May 2015; accepted 4 June 2015; published online 30 June 2015

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www.bjcancer.com | DOI:10.1038/bjc.2015.238

More recently, a prespecified interim analysis of the results from an upfront phase III clinical trial in newly diagnosed glioblastoma patients, comparing NovoTTF-100A plus adjuvant temozolomide vs adjuvant temozolomide alone, revealed significantly improved patient outcome with a respective progression-free survival of 7.1 vs 4.0 months and OS of 19.6 vs 16.6 months (Stupp *et al*, 2014). Compared with newly diagnosed glioblastomas, patients with recurrent glioblastoma likely have several factors that led to a worse outcome, including clonal evolution of the tumour, evasion of the immune system and reduction of immune competence because of prior exposure to chemotherapy.

Dexamethasone is commonly used to treat neurologic symptoms caused by the glioblastoma (Vecht *et al*, 1994). However, it also has a plethora of systemic toxicities, including gastrointestinal haemorrhage with or without perforation, infection, and hyperglycaemia (Heimdal *et al*, 1992). Although dexamethasone has not been shown to interfere directly with the efficacy of treatments against glioblastoma, there is emerging evidence from both preclinical and clinical data in other malignancies to suggest that dexamethasone may affect the patient's antitumour immunity. First, although the immune system has evolved multiple mechanisms to recognise and eliminate neoplastic cells (Senovilla *et al*, 2013), tumours emerge within the patient when they escape immune surveillance (Mittal *et al*, 2014). At this point, the tumour further subverts the immune system by eliciting normal wound healing and tissue remodelling responses, whereas promoting a state of immune privilege within the tumour microenvironment (Schreiber *et al*, 2011). In this setting, dexamethasone may potentiate existing local immunosuppression via global induction of I κ B α and inhibition of NF- κ B activity in lymphocytes, resulting in global immunosuppression (Auphan *et al*, 1995). Second, dexamethasone can lower the number of CD4⁺ lymphocytes in newly diagnosed patients with glioblastoma treated with radiation alone or in combination with temozolomide, and this attenuated CD4⁺ lymphocyte count is associated with increased infections and decreased survival (Hughes *et al*, 2005; Grossman *et al*, 2011). Lastly, recent clinical trial data have shown that there were more systemic and central nervous system responders to ipilimumab, an immune checkpoint inhibitor, in the cohort taking no dexamethasone as compared with the cohort taking dexamethasone, suggesting that dexamethasone interferes with the efficacy of ipilimumab (Margolin *et al*, 2012).

In this paper, we present evidence that immune suppression by dexamethasone markedly interferes with the clinical efficacy of two disparate therapies for recurrent glioblastoma: electric field-based therapy delivered by the NovoTTF-100A as well as conventional chemotherapies. Unlike prior clinical trials, the cohort treated with TTF field monotherapy offered us an opportunity to study unambiguously the effect of dexamethasone on patient survival unencumbered by concurrent chemotherapies that suppress the immune system. We also present data that strongly support a role for immune competence in effecting TTF field treatment by analyzing T-cell subsets measured in a separate cohort of patients for validation.

PATIENTS AND METHODS

Patients. Subjects signed informed consent from their respective treating institutions before participation in the phase III trial comparing NovoTTF-100A vs BPC chemotherapy (Ponkem and Wong, 2012; Stupp *et al*, 2012). A *post hoc* analysis of the dexamethasone effect on the two cohorts was performed based on anonymised data obtained from the sponsor, from whom the corresponding author had full access to the primary data. The outcome of the analysis was then validated retrospectively, under

an institutional review board-approved protocol from Dana Farber/Harvard Cancer Center (protocol no. 12-519), using a separate cohort of patients who were treated with NovoTTF-100A and bevacizumab at Beth Israel Deaconess Medical Center.

Statistical analysis. Statistical analyses were performed by using R statistics base package (<http://www.r-project.org>) and its libraries. Two-tailed Wilcoxon's rank-sum test with continuity correction was used to determine whether two independent groups of data were statistically different from each other. A modified binary search algorithm (Knuth, 1971; Tondel *et al*, 2002), written in R, was used to iteratively partition data in both two and three dimensions. The Loess local nonparametric polynomial regression was used to perform curve fitting of the OS as a function of dexamethasone dose (Cleveland, 1979; Shipley and Hunt, 1996; Cleveland and Loader, 1996) and OS was analyzed using Kaplan-Meier statistics (Kaplan and Meier, 1958).

RESULTS

Effect of dexamethasone on TTF field therapy and BPC chemotherapy. Our previous *post hoc* analysis of responders in the phase III trial demonstrated that responders to TTF field therapy required significantly lower doses of dexamethasone compared with non-responders (Wong *et al*, 2014). We therefore investigated further whether there was a threshold dose of dexamethasone that affected outcome within the entire trial population. Using an unsupervised binary partitioning algorithm (Knuth, 1971; Tondel *et al*, 2002), we stratified the TTF field therapy cohort based on the dexamethasone dose that yielded the greatest statistical difference in median OS. The results revealed that subjects who used >4.1 mg per day dexamethasone ($n=64$) exhibited a significantly shortened median OS of 4.8 months (95% confidence interval (CI): 3.9–6.0) vs those who used ≤ 4.1 mg per day ($n=56$), with a median OS of 11.0 months (95% CI: 8.8–16.6) ($\chi^2=34.6$, $P<0.0001$; Figure 1A). We then used the same dexamethasone cutoff to stratify control patients in the BPC chemotherapy cohort and observed a similar, albeit less robust, dichotomisation, with a respective median OS of 6.0 months (95% CI: 3.5–8.3) ($n=54$) vs 8.9 months (95% CI: 7.2–16.1) ($n=63$) ($\chi^2=10.0$, $P=0.0015$; Figure 1B) for those receiving >4.1 vs ≤ 4.1 mg per day of dexamethasone, respectively. There are two potential explanations for these results: either patients with larger, more aggressive tumours required a higher dose of dexamethasone for symptom control or doses of dexamethasone >4.1 mg per day interfered with both therapeutic interventions used in this trial. However, tumour size did not differ statistically between patient cohorts that used dexamethasone at either >4.1 or ≤ 4.1 mg per day (Figures 1C and D). Therefore, factors other than tumour size influence the OS of subjects receiving high vs low doses of dexamethasone.

To further investigate the effect of dexamethasone on patient outcome, we compared the survival characteristics of the cohort treated with TTF field therapy to the one treated with BPC chemotherapy in the respective dexamethasone dosage groups. First, we compared the two treatment groups when the dosage of dexamethasone used was ≤ 4.1 mg per day. Although the two OS curves overlapped ($\chi^2=0.9$, $P=0.3510$; Figure 2A), we detected a marked separation between these two curves at time points less than the median OS. Indeed, when we compared the survival curves of the two cohorts for subjects who used dexamethasone ≤ 4.1 mg per day and possessed survival times of less than the median OS, we found a significant difference between the two subgroups, with a median OS of 6.6 (range 1.4–10.1) months for the TTF field-treated subgroup ($n=31$) vs 3.9 (range 0.0–8.6) months for the BPC chemotherapy-treated subgroup ($n=40$) ($P=0.0015$; Figure 2C). However, for subjects who lived longer

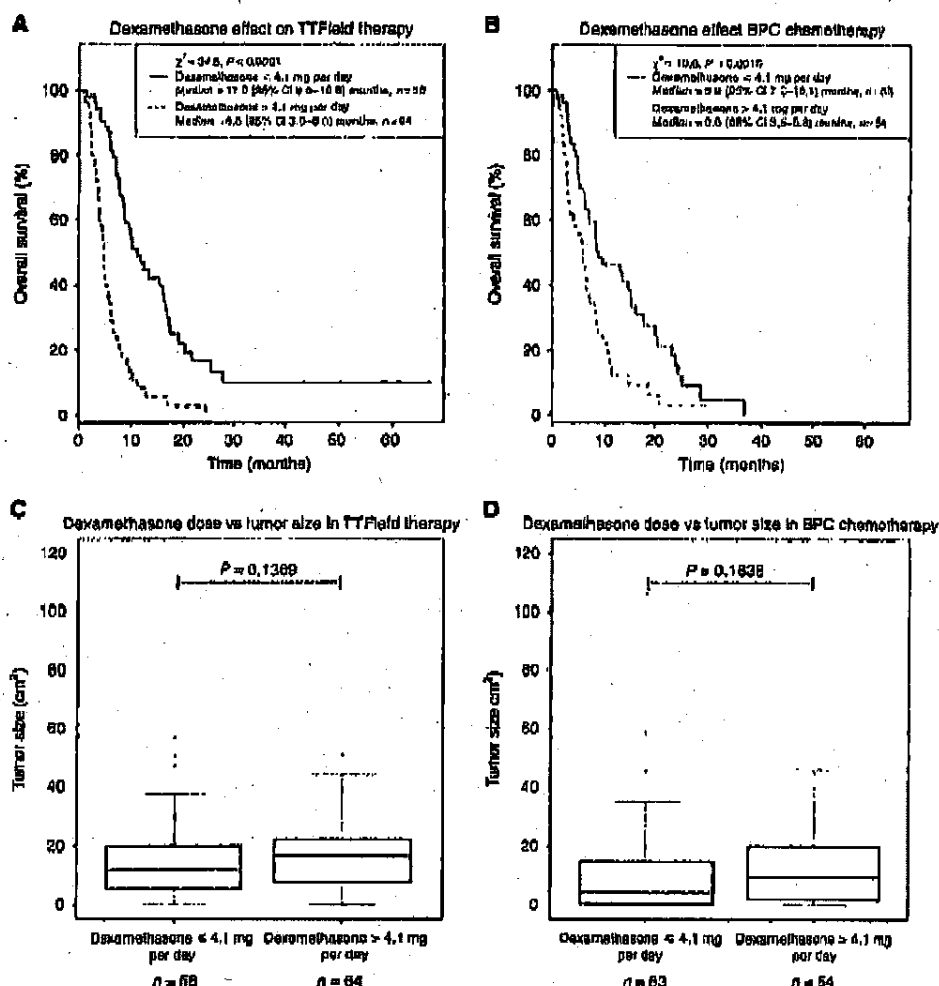


Figure 1. Kaplan-Meier OS and tumour size with respect to dexamethasone requirement of ≤ 4.1 vs > 4.1 mg per day from subjects enrolled in the phase III trial comparing TTField therapy vs BPC chemotherapy. (A) Subjects enrolled in the TTField treatment arm taking dexamethasone ≤ 4.1 (solid blue) vs > 4.1 (dashed blue) mg per day, which was determined by an unsupervised binary partitioning algorithm. Subjects who used ≤ 4.1 mg per day of dexamethasone ($n = 56$) had a median OS of 11.0 months (95% CI: 8.8–16.6) as compared with those who used > 4.1 mg per day ($n = 64$) had a median OS of 4.8 months (95% CI: 3.9–6.0) ($\chi^2 = 34.6$, $P < 0.0001$). (B) Subjects enrolled in the BPC chemotherapy arm taking dexamethasone ≤ 4.1 (solid red) vs > 4.1 (dashed red) mg per day was determined by the same unsupervised binary partitioning algorithm. Subjects who used ≤ 4.1 mg per day of dexamethasone ($n = 63$) had a median OS of 8.9 months (95% CI: 7.2–16.1) as compared with those who used > 4.1 mg per day ($n = 54$) had a median OS of 6.0 months (95% CI: 3.5–8.3) ($\chi^2 = 10.6$, $P = 0.0019$). (C) Box-and-whisker plot of bidimensional tumour size in the TTField therapy cohort that received dexamethasone ≤ 4.1 vs > 4.1 mg per day. Subjects who took dexamethasone ≤ 4.1 mg per day ($n = 56$) had a median tumour size of 11.9 (range 0.0–56.7) cm^2 as compared with those who used > 4.1 mg per day ($n = 64$) had a median tumour size of 16.8 (range 0.3–51.0) cm^2 ($P = 0.1369$). (D) Box-and-whisker plot of bidimensional tumour size in the BPC chemotherapy cohort that received dexamethasone ≤ 4.1 vs > 4.1 mg per day. Subjects who took dexamethasone ≤ 4.1 mg per day ($n = 63$) had a median tumour size of 4.2 (range 0.0–11.2) cm^2 as compared with those who used > 4.1 mg per day ($n = 54$) had a median tumour size of 9.6 (range 0.0–46.0) cm^2 ($P = 0.1638$).

than the median OS, there was no difference in the OS curves, with a median OS of 16.7 (range 11.0–66.9) months for the TTField-treated subgroup ($n = 25$) vs 16.8 (range 8.9–36.7) months for the BPC chemotherapy-treated subgroup ($n = 23$) ($P = 0.5773$; Figure 2E). In contrast, among subjects who received high dexamethasone doses of > 4.1 mg per day, the overlapping OS curves ($\chi^2 = 1.5$, $P = 0.2240$; Figure 2B) appeared to diverge for the subjects whose survival were greater than the median OS. Remarkably, the TTField-treated subgroup was worse compared with the BPC chemotherapy-treated subgroup when treated with

dexamethasone doses > 4.1 mg per day, with a respective median OS of 6.7 (range 4.8–24.3) months ($n = 29$) vs 8.7 (range 6.0–29.6) months ($n = 22$) ($P = 0.0097$; Figure 2D). However, for subjects whose survival were less than the median OS and used > 4.1 mg per day dexamethasone, there was no difference between the TTField-treated and the BPC chemotherapy-treated subgroups, with the former having a median OS of 3.0 (range 0.8–4.5) months ($n = 35$) as compared with the latter having a median OS of 2.8 (range 0.2–5.8) months ($n = 32$) ($P = 0.8456$; Figure 2B). Collectively, the data in Figures 2C and D indicate that the extent

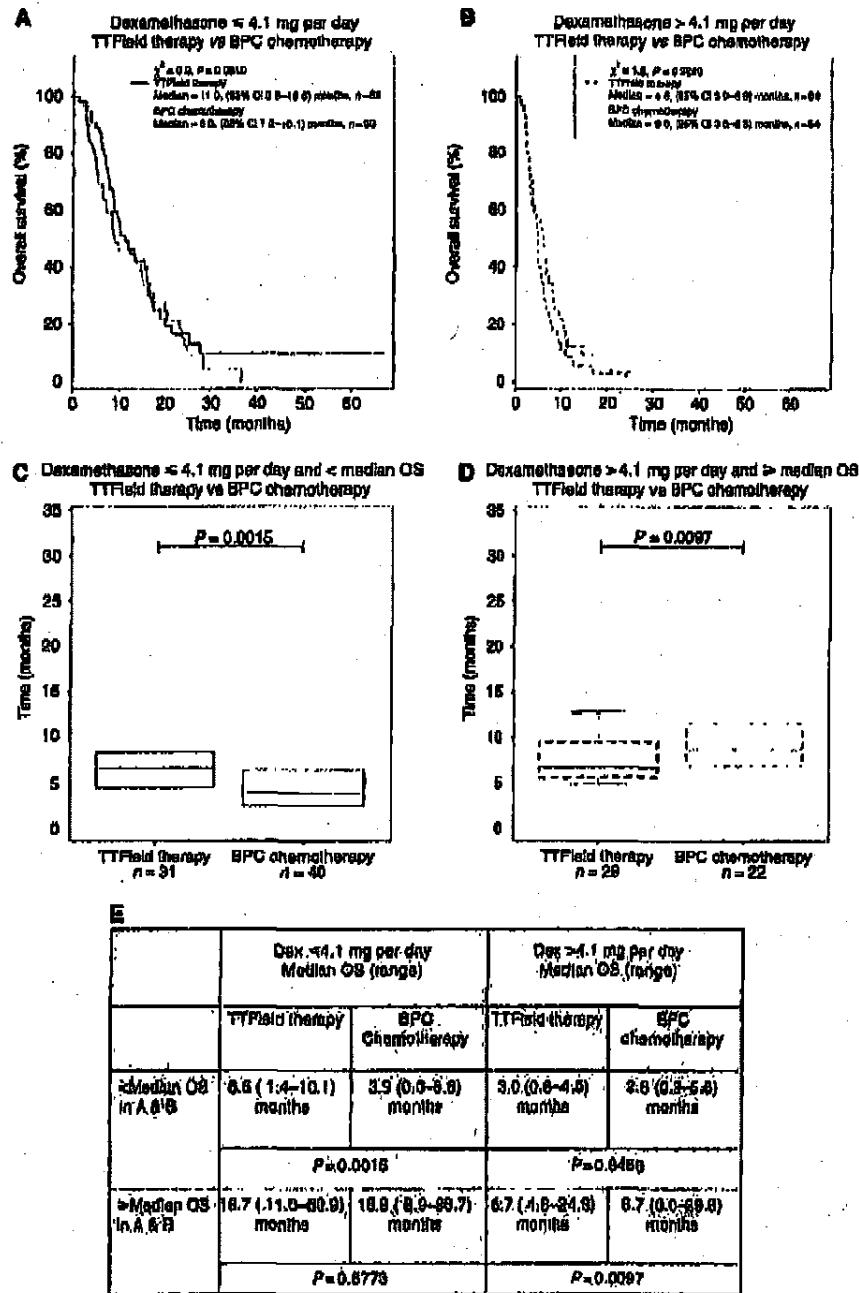


Figure 2. Comparison of OS in subjects treated with TTField therapy vs BPC chemotherapy segregated by dexamethasone usage. (A) Comparison of subjects using dexamethasone ≤ 4.1 mg per day in both TTField therapy (blue) and BPC chemotherapy (red) arms. (B) Comparison of subjects using dexamethasone > 4.1 mg per day in both TTField therapy and BPC chemotherapy arms. (C) Box-and-whisker plot of OS between TTField vs BPC chemotherapy-treated subjects using ≤ 4.1 mg per day of dexamethasone and $<$ the median OS in (A). The median OS was 6.6 months (range 1.4–10.1) for TTField-treated subjects ($n = 31$) vs 3.9 months (range 0.0–8.6) for BPC chemotherapy-treated subjects ($n = 40$) ($P = 0.0015$). (D) Box-and-whisker plot of OS between TTFields vs BPC chemotherapy-treated subjects using > 4.1 mg per day of dexamethasone and \geq the median OS in (B). The median OS was 6.7 months (range 4.8–24.3) for TTField-treated subjects ($n = 29$) vs 6.7 months (range 6.0–29.6) for BPC chemotherapy-treated subjects ($n = 22$) ($P = 0.0097$). (E) Median OS, range, and P -values for the four subgroups: (i) dexamethasone ≤ 4.1 mg per day and $<$ median OS in (A), (ii) dexamethasone > 4.1 mg per day and $<$ median OS in (B), (iii) dexamethasone ≤ 4.1 mg per day and \geq median OS in (A), and (iv) dexamethasone > 4.1 mg per day and \geq median OS in (B).

of dexamethasone exposure not only predicted treatment efficacy but also strongly suggest that TTField therapy is superior to BPC chemotherapy in the setting of low dexamethasone usage. However, under the influence of higher dexamethasone usage, the benefit of TTField therapy appeared to be negated to a greater extent when compared with BPC chemotherapy as if TTField-treated subjects were not provided with any therapy at all.

Dose-dependent effect of dexamethasone on treatment efficacy. We next asked whether or not dexamethasone has a dose-dependent influence on treatment efficacy by analysing the entire dose spectrum used in the trial. We partitioned the TTField-treated cohort using a dexamethasone dose cutoff from 0.0 to 37.0 mg per day, plotted the respective median OS of the groups at \leq cutoff or $>$ cutoff vs successive dexamethasone dosages, and fitted the data with the best curves using the nonparametric Loess local polynomial regression (Figure 3) (Cleveland, 1979; Cleveland and Loader, 1996; Shipley and Hunt, 1996). In addition, we plotted the log-rank *P*-values of the dichotomised groups in each successive dexamethasone dosage and found two nadir *P*-values of 0.00000008 and 0.00002524 corresponding to dexamethasone doses of 4.1 and 7.8 mg per day, respectively. We observed that there was decremental OS starting at a dexamethasone dose of 4.1 mg per day and, with successive increases of dexamethasone, reached an inflection point at 7.8 mg per day, after which the rate of OS decreased slowly (Figure 3A).

We also performed the same dose-dependent analysis of dexamethasone in the BPC chemotherapy-treated cohort and found a nadir *P*-value of 0.00163291 at 3.3 mg per day and another of 0.00011858 at 7.5 mg per day. Similarly, the best-fit curve derived in Figure 3B also suggests that the dexamethasone dose near 4 mg per day may also represent a point at which decremental OS can be observed with successive increases in dexamethasone dosage. This progressive decrement in OS occurred with successive increases of dexamethasone until an inflection point is observed at a dose near 7.5 mg per day, after which the rate of OS decreased slowly. Taken together, both cohorts experienced interference from dexamethasone at a dose near 4.0 mg per day and a maximal effect was observed near 7.5 mg per day.

Validation of the dexamethasone effect on TTField-treated patients from a single institution. We next proceeded to validate the observed dexamethasone effect on patient outcome within the trial by retrospectively analysing our own single-institution cohort. From November 2012 to February 2014, we treated 38 patients (Table 1) using TTField monotherapy as treatment or in combination with bevacizumab, whereas dexamethasone usage was aggressively reduced. Three patients who were referred specifically to our institution did not receive TTField therapy because of patient choice of other treatments, severe medical comorbidities, or advanced intracranial disease that was deemed more suitable for hospice care. Among the remaining 35 patients, their median OS was 4.3 months (95% CI: 3.5–8.7). To properly compare this cohort with the subjects enrolled in the phase III trial, we included only those with a KPS \geq 70 or greater ($n = 23$) in our validation set. This sub-population exhibited a median OS of 8.0 months (95% CI: 3.8–13.8) compared with 3.2 months (95% CI: 1.4–NA) for the remaining patients with a KPS $<$ 70 ($n = 12$) ($\chi^2 = 8.5$, $P = 0.0035$; Figure 4A). We then applied a cutoff of dexamethasone 4.1 mg per day as was found in our previous binary partitioning analysis. Patients who used dexamethasone \leq 4.1 mg per day had a significantly longer OS compared with those who used $>$ 4.1 mg per day, with a median OS of 8.7 months (95% CI: 6.7–NA) ($n = 19$) vs 3.2 months (95% CI: 1.2–NA) ($n = 4$), respectively ($\chi^2 = 11.1$, $P = 0.0009$; Figure 4B). Although our single-institution cohort has fewer patients compared with the cohorts in the phase III trial, we nevertheless observed a robust segregation of OS in the patient groups, validating the previously observed effect of dexamethasone on patient outcome.

Comparison of patients within the validation cohort with a KPS \geq 70 and dexamethasone usage \leq 4.1 mg per day ($n = 19$) to the phase III TTField therapy cohort who used dexamethasone \leq 4.1 mg per day ($n = 56$, from Figure 2A) revealed no statistical difference between the two groups, with a median OS of 8.7 months (95% CI: 6.7–NA) vs 11.0 months (95% CI: 8.8–16.6), respectively ($\chi^2 = 2.1$, $P = 0.1520$; Figure 4C). We next asked whether important prognostic factors within our cohort varied relative to patients within the phase III cohort by examining the possible effects of age and tumour size. The median age of our

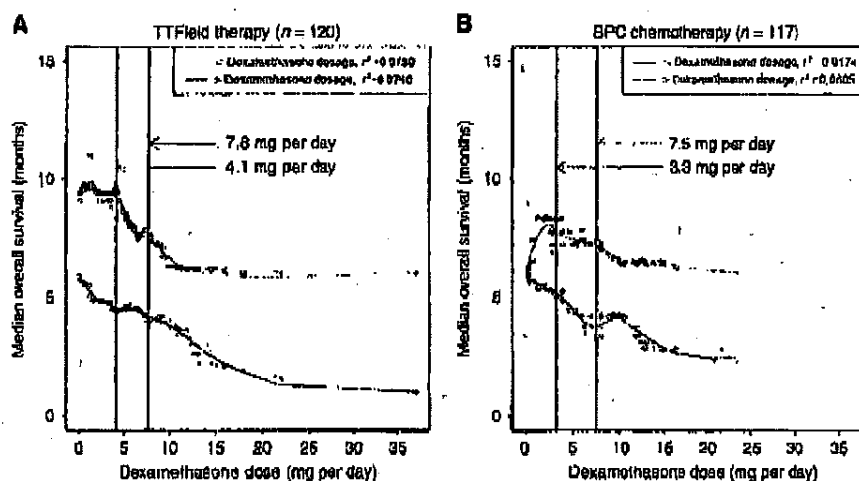


Figure 3. Loess local polynomial regression of median OS vs dexamethasone dose. Dexamethasone was treated as a discrete variable successively and the median OS was plotted for the group \leq (green) and $>$ (blue) compared with the variable dosage of dexamethasone. Curve fitting was performed using the Loess local polynomial regression. (A) In the TTField therapy cohort ($n = 120$), there was decremental OS from 4.1 mg per day that reached an inflection point at 7.8 mg per day, after which the rate of OS decrease slowed. (B) In the BPC chemotherapy cohort ($n = 117$), there was decremental OS from 3.3 mg per day that reached an inflection point at 7.5 mg per day, after which the rate of OS decrease slowed.

Table 1. Patient characteristics in the validation cohort and the NovoTTF-100A cohort in phase III trial

| Patient characteristics | Validation cohort (n = 35) | NovoTTF-100A cohort (n = 120) | P-value |
|--------------------------------------------------|----------------------------|-------------------------------|---------|
| Age (range) | 57 (30–77) years | 54 (24–80) years | |
| Gender | | | |
| Male | 22 (63%) | 92 (77%) | |
| Female | 13 (37%) | 28 (23%) | |
| Karnofsky performance status | | | |
| Median | 70 (range 50–90) | 80 (range 50–100) | |
| Tumour size, bidimensional | | | |
| T1 Gad, median (range) (cm ²) | 12.2 (0.3–40.6) | 14.2 (0.0–56.7) | 0.6178 |
| FLAIR, median (range) (cm ²) | 35.2 (7.0–90.9) | N/A | |
| Dexamethasone dose | | | |
| Median (range) (mg per day) | 3.0 (0.0–15.0) | 4.7 (0.0–37.5) | |
| Absolute T-cell subsets | | | |
| CD3, median (range) (cells per mm ³) | 733 (0–1458) | N/A | |
| CD4, median (range) (cells per mm ³) | 414 (25–788) | N/A | |
| CD8, median (range) (cells per mm ³) | 302 (44–1039) | N/A | |
| Prior therapy | | | |
| First recurrence | 6 (17%) | 11 (9%) | |
| Second recurrence | 10 (29%) | 58 (48%) | |
| Third recurrence | 19 (54%) | 51 (43%) | |
| Prior bevacizumab | 25 (71%) | 23 (19%) | |
| Outcome | | | |
| Overall survival, median (months) | 4.3 (95% CI: 3.5–8.7) | 7.1 (95% CI: 6.1–8.8) | 0.0468 |

Abbreviations: CI = confidence interval, FLAIR = fluid-attenuated inversion recovery, Gad = gadolinium, N/A = not applicable, TTF = tumour treating alternating electric field.

cohort was 57 (range 30–77) years and it is not different from the median age of 54 (range 24–80) years in the TTF-treated cohort from the phase III trial (Stupp *et al*, 2012). Average tumour size in our cohort as measured by gadolinium-enhanced T1-weighted MRI showed a median bidimensional measurement of 12.2 (range 0.3–40.6) cm², which is similar to the median bidimensional measurement of 14.2 (0.0–56.7) cm² in the TTF-treated phase III cohort ($P = 0.6178$; Table 1). However, 15 of 23 patients (65%) were already on bevacizumab before their neuroimaging studies, possibly interfering with tumour measurement because bevacizumab can reduce vascular permeability in tumours causing decreased gadolinium enhancement (Wong and Brem, 2008). Further, blockade of vascular endothelial growth factor can promote an invasive and diffuse glioblastoma phenotype that result in tumours possessing greater size than can be measured on gadolinium-enhanced T1-weighted MRI (Norden *et al*, 2008; Lu *et al*, 2012). We therefore measured the bidimensional size of the FLAIR abnormality. Indeed, in our cohort, the median bidimensional FLAIR abnormality was 29.6 (range 7.0–60.2) cm², which is more than two times the tumour size observed on gadolinium-enhanced T1-weighted MRI in the phase III trial (Stupp *et al*, 2012). As expected, this bevacizumab effect on tumour measurement was corroborated in our entire patient cohort ($n = 38$) by the strong correlation between the size of the gadolinium-enhanced T1-weighted and FLAIR measured bidimensional tumour size among those not on bevacizumab ($r^2 = 0.7333$, $n = 10$; Supplementary Figure 1A), whereas no such correlation was seen among those on bevacizumab ($r^2 = 0.1446$, $n = 27$; Supplementary Figure 1B). Furthermore, we found that patients in our validation cohort who used dexamethasone > 4.1 mg per day ($n = 4$) had a worse outcome compared with the corresponding cohort in the phase III trial ($n = 64$), with a median OS of 3.2 months (95% CI: 1.2–NA) vs 4.8 months (95% CI: 3.9–6.0), respectively ($\chi^2 = 6.3$, $P = 0.0121$; Figure 4D). Therefore, our single-institution validation cohort, who had KPS ≥ 70 , used dexamethasone ≤ 4.1 mg per day and possessed greater tumour burden, compared favourably with those treated with TTFs therapy in the phase III trial, but those with KPS ≥ 70 but used

dexamethasone > 4.1 mg per day probably suffered from a worse outcome compared with the corresponding trial cohort.

Patient immune characteristics and TTF therapy efficacy. Dexamethasone has been associated with profound immunosuppression (Hughes *et al*, 2005; Grossman *et al*, 2011) and it may severely limit a patient's ability to mount an antitumour immune response against the glioblastoma (Zitvogel *et al*, 2008a). Our data clearly demonstrated that dexamethasone doses higher than a threshold level of 4.1 mg per day correlated with a poorer patient outcome during TTF therapy. This finding strongly suggests an immunological component behind the efficacy of this intervention and that factors required for general immune competence may have a role in predicting therapeutic outcome in our patients. We therefore analysed their CD3⁺, CD4⁺, and CD8⁺ T-lymphocyte counts during the course of their treatment. Using the unsupervised binary partitioning approach described above for dexamethasone dose, we attempted to identify whether there was any threshold for the absolute CD3⁺, CD4⁺, or CD8⁺ T-lymphocyte count, which yielded the greatest statistical difference in OS when used to stratify our patient population. Significantly, this analysis revealed that the median OS of patients with absolute CD3⁺ ≤ 382 cells per mm³ was 2.0 months (95% CI: 1.2–NA) ($n = 7$). In contrast, the median OS of those with CD3⁺ > 382 cells per mm³ was 7.6 months (95% CI: 4.3–13.9) ($n = 22$) ($\chi^2 = 17.8$, $P < 0.0001$; Figure 5A), with the data showing that patient survival was positively correlated with the absolute numbers of CD3⁺ T lymphocytes. Similarly, we found that patients with absolute CD4⁺ ≤ 236 cells per mm³ exhibited a median OS of 2.7 months (95% CI: 1.4–NA) ($n = 9$) as compared with those with CD4⁺ > 236 cells per mm³ with a median OS of 8.0 months (95% CI: 4.6–NA) ($n = 20$) ($\chi^2 = 13.4$, $P = 0.0002$; Figure 5B). Furthermore, patients with an absolute CD8⁺ count of ≤ 144 cells per mm³ exhibited a median OS of 2.0 months (95% CI: 2.0–NA) ($n = 5$) as compared with 6.8 months (95% CI: 3.9–13.8) ($n = 24$) for those with CD8⁺ > 144 cells per mm³ ($\chi^2 = 8.1$, $P = 0.0045$; Figure 5C).

We next asked whether CD3⁺, CD4⁺, and CD8⁺ lymphocyte counts was related to the overall status of the patient's peripheral

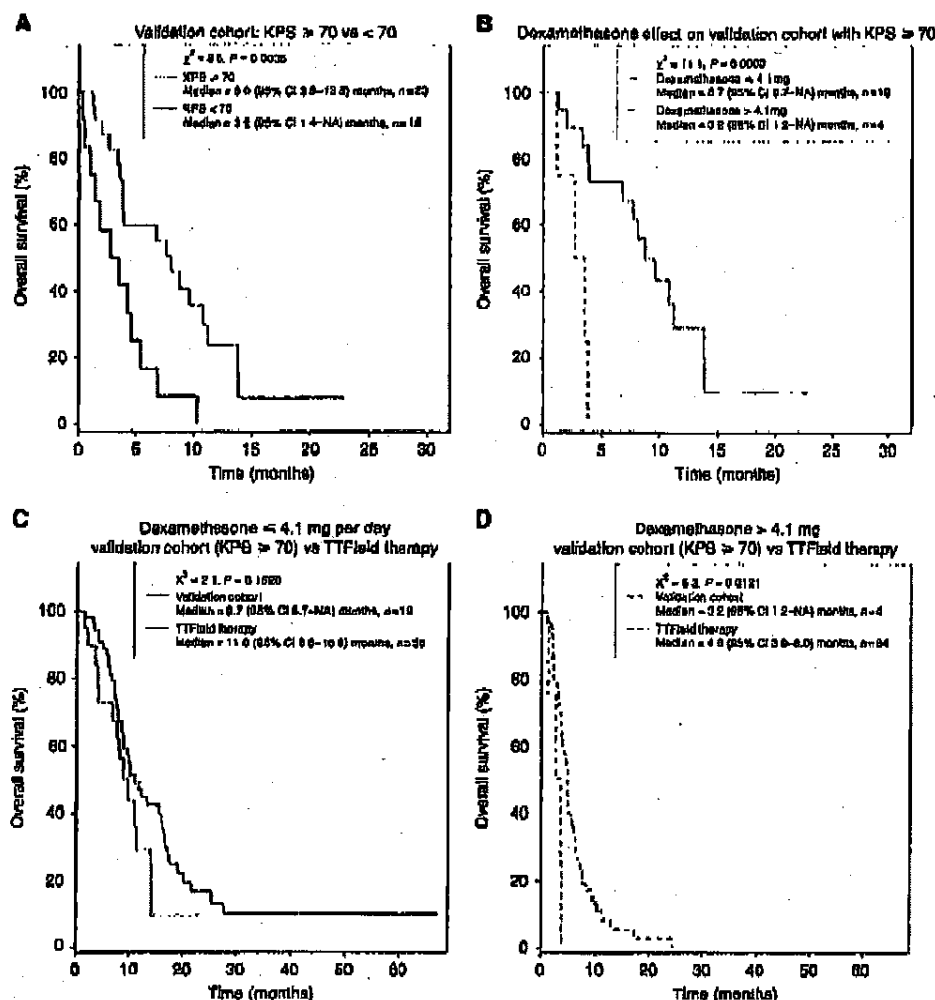


Figure 4. Kaplan-Meier estimates of survival in the validation cohort from a single institution. (A) The Kaplan-Meier survival curves for patients with KPS ≥ 70 (solid green) vs those with KPS < 70 (solid black). (B) Dexamethasone effect on the cohort with KPS ≥ 70 by comparing patients taking dexamethasone ≤ 4.1 (solid green) vs those taking > 4.1 mg per day (dashed green). (C) Comparison of the TTField-treated subjects who used ≤ 4.1 mg per day of dexamethasone in the phase III trial (from Figure 2A) vs the validation cohort with having KPS ≥ 70 and taking dexamethasone ≤ 4.1 mg per day. (D) Comparison of the TTField-treated subjects who used > 4.1 mg per day of dexamethasone in the phase III trial (from Figure 2B) vs the validation cohort with having KPS ≥ 70 and taking dexamethasone > 4.1 mg per day.

blood counts and dexamethasone requirement. As expected, there was a correlation between CD3⁺ and CD4⁺ cells ($r^2 = 0.6949$) and between CD3⁺ and CD8⁺ cells ($r^2 = 0.5001$) but not between CD4⁺ and CD8⁺ cells ($r^2 = 0.0733$). However, there was no correlation between white blood cells (WBC) and CD3⁺ cells ($r^2 = 0.0053$), WBC and CD4⁺ cells ($r^2 = 0.0023$), and WBC and CD8⁺ cells ($r^2 = 0.0032$). No correlation was also detected between platelets and CD3⁺ cells ($r^2 = 0.2576$), platelets and CD4⁺ ($r^2 = 0.2746$), and platelets and CD8⁺ ($r^2 = 0.0887$). Similarly, there was no correlation between the daily dexamethasone dose and CD3⁺ cells ($r^2 = 0.1888$), dexamethasone and CD4⁺ cells ($r^2 = 0.1531$), and dexamethasone and CD8⁺ cells ($r^2 = 0.0451$). Taken together, CD3⁺, CD4⁺, and CD8⁺ lymphocyte counts appear to be independent of the peripheral blood counts and dexamethasone dose effect. Therefore, T-lymphocyte counts may serve as an independent measure of immunocompetence in our patients and predict treatment outcome when using NovoTTF-100A.

DISCUSSION

Our previous *post hoc* analysis of responders in the phase III trial comparing NovoTTF-100A monotherapy and BPC chemotherapy for recurrent glioblastoma revealed that dexamethasone and prior low-grade glioma histology were predictors of response (Wong *et al.*, 2014). Traditionally, oncologists view dexamethasone's influence on glioblastoma patients from the perspective of its antioedema effect from the tumour (Vecht *et al.*, 1994), antiemetic efficacy against emetogenic chemotherapies, infections from its systemic immunosuppressive property (Vecht *et al.*, 1994; Hughes *et al.*, 2005), and changes in contrast enhancement on computed tomography (Chamberlain *et al.*, 1986) or MRI (Ostergaard *et al.*, 1999). Because dexamethasone has the potential to produce profound toxicities in patients in large part by suppressing their immune system and it is a clinically modifiable factor, we therefore extended our analysis of possible dexamethasone effect on outcome

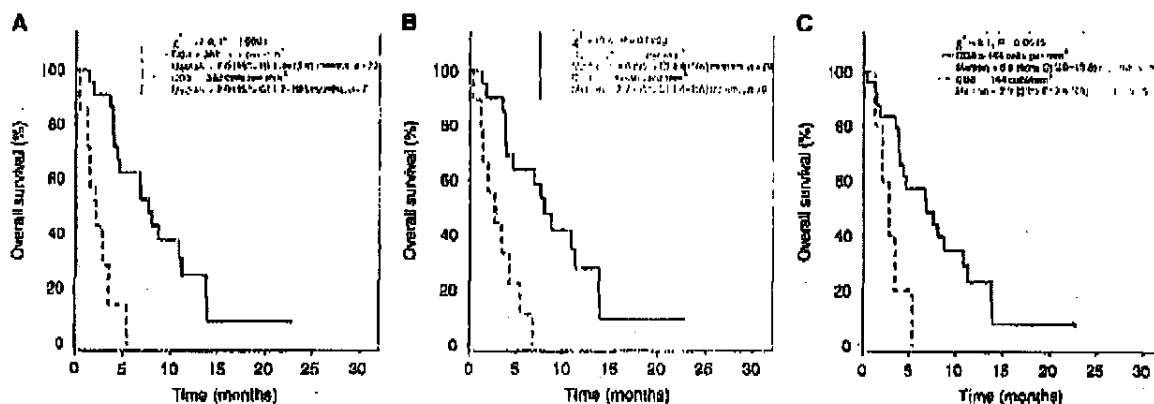


Figure 5. Wilcoxon's rank-sum test of the optimal cutoff T-lymphocyte subsets as determined by an unsupervised binary partitioning algorithm. (A) Median OS of patients with absolute $CD3^+$ ≤ 382 vs > 382 cells per mm^2 was 2.0 months (range 0.3–5.4) ($n = 7$) and 7.7 months (range 1.3–22.7) ($n = 25$), respectively ($P = 0.0017$). (B) Median OS of patients with absolute $CD4^+$ ≤ 236 vs > 236 cells per mm^2 was 2.7 months (range 0.3–6.7) ($n = 9$) and 8.0 months (range 1.3–22.7) ($n = 23$), respectively ($P = 0.0029$). (C) Median OS of patients with absolute $CD8^+$ ≤ 144 vs > 144 cells per mm^2 was 2.7 months (range 1.2–5.4) ($n = 5$) and 7.6 months (range 0.3–22.7) ($n = 27$), respectively ($P = 0.0313$).

to the entire trial cohort. In this study, we have uncovered compelling evidence that dexamethasone counteracted the therapeutic efficacy of TTFields. Further, we also found that its use negatively correlated with survival in the cohort treated with chemotherapy. Our analysis is the first to show this significant impact of dexamethasone on treatment efficacy and patient OS, which is a discrete and unequivocal endpoint in contrast to progression-free survival or response for the conduct of clinical trials for recurrent glioblastomas.

In contrast to commonly used chemotherapeutic regimens, TTField monotherapy does not exert deleterious effects on the immune system, and thus, unlike the chemotherapy-treated cohort, TTField-treated subjects did not receive concurrent immunosuppressive agents other than dexamethasone during the entire trial period. Therefore, this trial provided us with a unique opportunity to examine the interference of dexamethasone on the clinical outcome of patients without the confounding influence of cytotoxic chemotherapies. Given our previous observation that responders from this trial had low dexamethasone usage (Wong *et al*, 2014), we first asked whether we could determine a threshold of dexamethasone exposure below which a benefit in patient survival could be detected within the entire cohort. Using an unsupervised mathematical algorithm, we found that a dexamethasone dose of 4.1 mg per day produced the greatest statistical segregation of OS in the TTField-treated cohort, and subjects who received > 4.1 mg per day had a 2.3-fold decrease in median OS compared with those who used ≤ 4.1 mg per day. Notably, using this dose level to stratify the control cohort treated with BPC chemotherapy also produced a statistically significant, but less robust, OS segregation, and subjects who received > 4.1 mg per day had a 1.5-fold decrease in median OS compared with those who used ≤ 4.1 mg per day. Within both cohorts, patients exhibited a decrease in OS starting at about 4.0 mg per day, with progressive decrement until a dosage of 8.0 mg per day, above which there was no further decrease in OS. Therefore, our data indicate that dexamethasone has a generalised and profound interference on treatment efficacy regardless of whether the treatment has non-cytotoxic or cytotoxic properties on the haematopoietic system.

Our analysis strongly indicates that dexamethasone interferes with the efficacy of both TTFields and BPC chemotherapies, the latter of which consisted largely of alkylating chemotherapies. In the sub-populations taking ≤ 4.1 mg per day of dexamethasone, 31 subjects treated with TTField monotherapy exhibited a better

outcome compared with the corresponding 40 subjects treated with BPC chemotherapy. This small but statistically significant benefit occurred within the first 11 months, after which the OS of the two cohorts overlapped and the benefit from TTField therapy dissipated. In contrast, for the sub-population taking > 4.1 mg per day of dexamethasone, 29 subjects treated with TTField monotherapy exhibited a worse outcome relative to the corresponding 22 subjects treated with BPC chemotherapy. Therefore, high dexamethasone dosage appears to negate or counteract the effect of both TTField therapy and BPC chemotherapy. Because the overall trial population in the TTField-treated cohort is only 120, the benefit of treatment in the 31 (26%) subjects taking ≤ 4.1 mg per day of dexamethasone is essentially negated by the hindrance caused by the 29 (24%) patients taking > 4.1 mg per day of dexamethasone when the populations were not segregated based on dexamethasone burden. This dexamethasone interference with TTField efficacy may explained the improved outcome seen in the trial for newly diagnosed glioblastoma patients (Slupp *et al*, 2014), who were not as severely affected by treatment effects when compared with recurrent glioblastoma patients who had a longer exposure to cytotoxic chemotherapy, dexamethasone, or both.

Our data also indicate that T-lymphocyte subsets may have an important role in the outcome of our validation cohort of patients treated with TTField therapy, with prolonged OS associated with absolute $CD3^+$ > 382 cells per mm^2 , $CD4^+$ > 235 cells per mm^2 , and $CD8^+$ > 144 cells per mm^2 in an unsupervised analysis. Hughes *et al* (2003) and Grossman *et al* (2011) both showed that dexamethasone induces a drop in $CD4^+$ lymphocyte count, which predisposes glioblastoma patients to infectious complications, and a $CD4^+$ count < 200 cells per mm^3 is associated with poor survival. However, we also noted that dexamethasone's immunosuppressive effect also blunted the therapeutic efficacy of TTField therapy and chemotherapy, probably as a result of its global interference with the patient's immune system. This notion is supported by our *in vitro* experiments, which demonstrated that cells attempting to divide in the presence of the TTFields are disrupted in mitosis during the metaphase-to-anaphase transition and experienced aberrant mitotic exit (Gera *et al*, 2015). These cells subsequently exhibited changes consistent with immunogenic cell death and thus were susceptible to immune elimination (Lee *et al*, 2011, 2013). Because subjects that received dexamethasone ≤ 4.1 mg per day in the phase III trial exhibited benefit from TTField therapy, the observed benefit is strongly consistent with an

increased immunogenicity of cells affected by TTFs. Furthermore, a number of cytotoxic chemotherapy agents, such as doxorubicin, 5-fluorouracil, and oxaliplatin, can induce either genomic or cytoplasmic stress in the tumour cell leading to immunogenic cell death (Zitvogel *et al.*, 2008b). Although the extent of immunostimulatory effects of alkylators, such as lomustine, carmustine, procarbazine, and temozolomide is unknown, dacarbazine has been shown to upregulate NKG2D ligands on tumour cells and thereby target them for immune elimination by natural killer (NK) cells and CD8⁺ cytotoxic T-lymphocytes (Hervieu *et al.*, 2013). Furthermore, alkylating agents have been shown to induce the secretion of ATP and HMGB1, both of which are danger signals that can activate immune responses against dying cells (Zong *et al.*, 2004). Lastly, in myeloma patients, dexamethasone can severely block lenalidomide-induced NK cell activation (Hsu *et al.*, 2011). Taken together, there is a strong indication from our data that the cytotoxic agents used in the trial against recurrent glioblastomas also act by inducing immune responses against the tumour and that concurrent dexamethasone usage negated this benefit.

There are a number of limitations in the interpretation of our findings. First, our data only allowed us to examine global immunosuppression in our patients but provide no means to assess local immunosuppression within the tumour microenvironment. This local suppression of immune surveillance is thought to be mediated by arginase, regulatory T cells, and myeloid-derived immunosuppressive cells (Facci *et al.*, 2006; Jacobs *et al.*, 2010; Raychaudhuri *et al.*, 2011). Nevertheless, removal of global immunosuppressive factors is the first step towards successful antiglioblastoma therapy. Second, our T-lymphocyte analysis only measured cells in the adaptive immune system. However, TTF therapy and certain chemotherapy agents could potentially induce an NK cell response against the glioblastoma (Hervieu *et al.*, 2013; Lee *et al.*, 2013). However, the observed dexamethasone effect on absolute CD3⁺, CD4⁺, and CD8⁺ lymphocytes could also negatively influence the activation of other cytotoxic subsets such as NK cells (Hsu *et al.*, 2011). Therefore, future analysis of the specific effects of dexamethasone on glioblastoma treatment would need to include the global effect on these cells.

In conclusion, dexamethasone exerted a profound interference on the therapeutic effects of both TTF therapy and BPC chemotherapies. The threshold dose at which dexamethasone was able to be used with minimal interference on these treatments was 4.1 mg per day or lower. In our validation set of TTF-treated patients, the cluster that had the longest OS had CD3⁺ > 382 cells per mm³, CD4⁺ > 236 cells per mm³, and CD8⁺ > 144 cells per mm³. Taken together, these data strongly suggest that the stimulation of immunity against the tumour operates in both of these therapeutic approaches. Future clinical trials for recurrent glioblastoma, as well as other types of brain tumours, may need to take into account the influence of dexamethasone on therapeutic outcome.

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Supplementary Information accompanies this paper on British Journal of Cancer website (<http://www.nature.com/bjc>)

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NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality

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Glioblastoma

Brain tumour

Chemotherapy

Randomised trial

Abstract *Purpose:* NovoTTF-100A is a portable device delivering low-intensity, intermediate frequency electric fields via non-invasive, transducer arrays. Tumour Treatment Fields (TTF), a completely new therapeutic modality in cancer treatment, physically interfere with cell division.

Methods: Phase III trial of chemotherapy-free treatment of NovoTTF (20–24 h/day) versus active chemotherapy in the treatment of patients with recurrent glioblastoma. Primary endpoint was improvement of overall survival.

Results: Patients (median age 54 years (range 23–80), Karnofsky performance status 80% (range 50–100) were randomised to TTF alone ($n = 120$) or active chemotherapy control ($n = 117$). Number of prior treatments was two (range 1–6). Median survival was 6.6 versus 6.0 months (hazard ratio 0.86 [95% CI 0.66–1.12]; $p = 0.27$), 1-year survival rate was 20% and 20%, progression-free survival rate at 6 months was 21.4% and 15.1% ($p = 0.13$), respectively in TTF and active control patients. Responses were more common in the TTF arm (14% versus 9.6%, $p = 0.19$). The TTF-related adverse events were mild (14%) or moderate (2%) skin rash beneath the transducer arrays. Severe adverse events occurred in 6% and 16% ($p = 0.022$) of patients treated with TTF and chemotherapy, respectively. Quality of life analyses favoured TTF therapy in most domains.

Conclusions: This is the first controlled trial evaluating an entirely novel cancer treatment modality delivering electric fields rather than chemotherapy. No improvement in overall survival was demonstrated, however efficiency and activity with this chemotherapy-free treatment device appears comparable to chemotherapy regimens that are commonly used for recurrent glioblastoma. Toxicity and quality of life clearly favoured TTF.

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1. Background

Glioblastoma is the most prevalent primary malignant brain tumour in adults. Median survival with optimal therapy is only 15 months from diagnosis, and most tumours recur within 9 months of initial treatment.¹ At the time of disease recurrence, treatment options for glioblastoma patients are limited. Repeat surgery may be considered in approximately 20% of patients,^{2,4} and re-irradiation is possible in rare circumstances. For most patients chemotherapy is indicated at disease recurrence, with the choice of drug varying greatly. In the United States, bevacizumab has been provisionally approved for recurrent glioblastoma, while the European Medicines Agency (EMA) rejected the application in the absence of a controlled trial.^{5,6} Cytotoxic agents most frequently used are alkylating agents like nitrosoureas (e.g. lomustine [CCNU] or carmustine [BCNU]),⁷ procarbazine⁸ or re-treatment with temozolomide.^{9,10} Response rates are below 10%, progression-free survival rates at 6 months <20%.^{7,8} In the absence of an established and satisfactory standard treatment, bevacizumab

alone and in combination with irinotecan and experimental treatments are commonly used.^{11–13}

Overall survival (OS) from recurrence is commonly short and without effective therapy rarely exceeds 3–5 months.^{14–19} In a randomised trial of repeat surgery with implantation of carmustine wafers versus placebo median survival was 6.5 versus 4.7 months.²⁰ With active therapy, a median survival of 7 months (range 5–9.2 months)^{7–10,12,13,21–24} has been reported. A recent randomised comparison of enzastaurin versus lomustine at first recurrence demonstrated a median survival of 7.1 months, with 19% of patients alive and progression-free at 6 months when treated with lomustine.⁷ Based on these results active chemotherapy as salvage treatment for patients with recurrent glioma is recommended, which strives to improve survival and quality of life despite inherent chemotherapy-related toxicity.

The NovoTTF-100A system (Novonure Ltd., Haifa, Israel) is a portable device delivering low intensity, intermediate frequency, alternating electric fields (Tumour Treating Fields; TTF) using non-invasive, disposable transducer arrays (Fig. 1A). These fields physically

Please cite this article as: Stupp R, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent Glioblastoma: A randomised phase III trial of a novel treatment modality. *Eur J Cancer* (2012), <http://dx.doi.org/10.1016/j.ejca.2012.04.011>

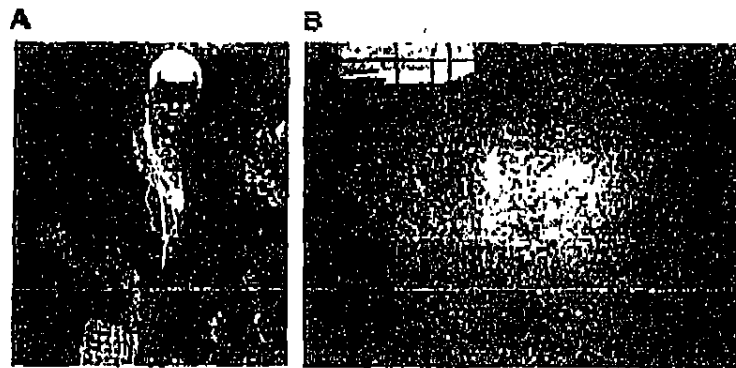


Fig. 1. Female patient wearing the portable NovoTTF-100A device (A). Grade 2 skin rash underneath transducer arrays in a different patient (B). With the patients' permission.

interfere with cell division by causing misalignment of microtubule subunits in the mitotic spindle during the metaphase to anaphase transition²⁵ and by dielectrophoretic movement of intracellular macromolecules and organelles during telophase.^{26,27} This causes failure of cytokinetic furrow formation and resultant mitotic blebbing, leading to the disruption of chromosome segregation and eventual cell death. The exact pathways by which spindle disruption and physical aggregation of macromolecules lead to cell death are unknown. TTF has been tested in several pilot clinical studies^{26,28,29} including a small single arm study as monotherapy for recurrent glioblastoma. The results of this pilot trial were promising³⁰ and served as the basis of this phase III trial comparing NovoTTF-100A monotherapy (TTF) to best active chemotherapy according to the physician's best choice (active treatment control group). This report describes for the first time the efficacy and safety of this entirely novel treatment modality compared to widely accepted active chemotherapies for the treatment of recurrent glioblastoma patients.

2. Methods

2.1. Patient selection

Patients 18 years or older with histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma) were eligible following radiologically confirmed disease progression (Macdonald criteria). Patients had a Karnofsky performance status $\geq 70\%$ and adequate hematologic, renal and hepatic function (absolute neutrophil count $\geq 1000/\text{mm}^3$; haemoglobin $\geq 100 \text{ g/L}$ platelet count $\geq 100,000/\text{mm}^3$; serum creatinine level $\leq 1.7 \text{ mg/dL}$ ($<150 \mu\text{mol/L}$); total serum bilirubin level \leq the upper limit of normal and liver function values, <3 times the upper limit of normal). Prior therapy must have included radiotherapy (with and without concomitant and/or adjuvant temozolomide). There was no limit on number or type of prior

therapies or recurrences. Patients with infra-tentorial tumour location were excluded, as were patients with implanted electronic medical devices (e.g. pacemaker, programmable ventriculo-peritoneal shunt). All patients provided written informed consent, and the study was approved by the institutional review boards or ethics committees of all participating centres.

2.2. Study design and treatment

Patients were randomised at a 1:1 ratio to receive either TTF monotherapy (without chemotherapy) or the best available active chemotherapy according to the local physician's choice (active control). Randomisation was performed using random block sizes and was stratified by centre and according to whether patients underwent surgery for their latest recurrence prior to trial entry. Assigned treatment had to start within 1 week of randomisation, and was to be continued until disease progression or intolerance.

For patients assigned to the TTF group four transducer arrays were placed on the patient's shaved scalp and connected to a portable, battery or power supply operated device (NovoTTF-100A) which was set to generate 200 kHz electric fields within the brain in two perpendicular directions (operated sequentially). Field intensity was set at $>0.7 \text{ V/cm}$ at the centre of the brain. Patients were trained on how to operate the device and then continued treatment at home. Treatment was continuous while maintaining normal daily activity. Transducer arrays were replaced by the patients, their caregivers or device technicians once or twice a week. Prior to placement, the scalp was shaved carefully with an electric razor in order to avoid skin wounding, transducer arrays were supplied sterile. Although uninterrupted treatment was recommended, patients were allowed to take treatment breaks of up to an hour, twice per day, for personal needs (e.g. shower). In addition, they were allowed to take 2–3 days off treatment at the end of each 4 weeks of treatment (which is the minimal

Please cite this article as: Stupp R, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised, phase III trial of a novel treatment modality. *Eur J Cancer* (2012), <https://doi.org/10.1016/j.ejca.2012.01.011>

required treatment duration for TTF therapy to reverse tumour growth).³⁰

Patients assigned to the active control received chemotherapy at the local investigator's discretion. The best available chemotherapy was prescribed according to local practice and depending on prior treatment exposure.

2.3 Patient surveillance and follow up

Baseline examinations included a gadolinium-enhanced magnetic resonance imaging (MRI) of the brain, full blood counts, blood chemistry tests, blood coagulation tests, electrocardiogram (ECG), physical examination including a detailed neurological examination and quality of life (QoL) questionnaire (European Organisation for Research and Treatment of Cancer (EORTC) QLQ C-30).

Patients were followed once a month, including laboratory tests. MRI was repeated every 2 months. QoL questionnaires were completed at baseline and then every 3 months. Tumour response and progression were determined by blinded central radiology review, according to Macdonald criteria.³¹ When an MRI could not be obtained, progression was assessed clinically based on neurological status, steroid dosing, adverse events and investigator assessment of progression.

Adverse events were recorded prospectively according to National Cancer Institute Common Toxicity Criteria (NCI CTC V3.0)

2.4 Statistical analysis

The primary end-point was OS. Secondary end-points were progression free survival (PFS), the percentage of patients alive and progression-free at 6 months (PPFS6), 1-year survival rate, radiological response rate (RR), QoL and safety. OS and PFS were computed from the day of randomisation until event or censored at last follow-up according to the Kaplan–Meier method, with 2-sided logrank statistics for comparison. The study had an 80 per cent power at a significance level of 0.05 to detect a 60 per cent increase in median OS (hazard ratio for death, 0.63). All analyses were performed using the intent to treat population of all randomised patients, patients lost to follow-up were censored at the time of last contact. A Cox proportional hazards model was used to adjust for confounding baseline variables (continuous and categorical). The survival data were tested for proportional hazards and the assumption of proportionality met. The Cox model was performed in two steps; first, all protocol pre-specified baseline variables were tested directly for interactions with OS; then a reduced model was performed testing the effect of all variables with significant interactions ($p < 0.05$) with OS together on the treatment effect of TTF versus active chemotherapy. Secondary end-points are presented without adjustment. QoL is pre-

sented as change from baseline to 3 months for each of the subscale domains and symptom scales of the QLQ-C30 questionnaire.

2.5 Organizational aspects

The trial was registered on www.clinicaltrials.gov, NCT#00379470. The trial was funded and sponsored by Novocure Ltd. Statistical analysis was performed by David Steinberg. The manuscript was written by Roger Stupp and Eilon Kirson, with substantial input by all co-authors. The final manuscript was reviewed and approved by all authors. The statistician and the corresponding author had unrestricted access to all data.

2.6 Role of the funding source

Representatives of the study sponsor were involved in the study design, data collection, data analysis, data interpretation and writing of the report. Data analysis was performed by David Steinberg, a compensated independent biostatistician. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Patients

From September 2006 until May 2009, 237 patients from 28 institutions in 7 countries were randomly assigned to receive TTF monotherapy (120 patients) or active control chemotherapy (117 patients). The baseline patient characteristics were balanced (Table 1). The median age was 54, and a quarter of the patients had undergone some surgical resection of the recurrent tumour prior to enrolment into the trial. More than 80% of patients had failed two or more prior lines of chemotherapy (≥second recurrence) and 20% of the patients had failed bevacizumab prior to enrolment. Histology was per local pathological diagnosis; in 8% a history of a prior lower grade glioma had been reported (secondary glioblastoma). *Methyl-guanine methyl-transferase (MGMT)* gene promoter methylation, an important predictive factor for benefit of temozolomide chemotherapy in newly diagnosed glioblastoma, was not assessed in this trial of patients with recurrent disease.

3.2. Patient disposition, treatment and compliance

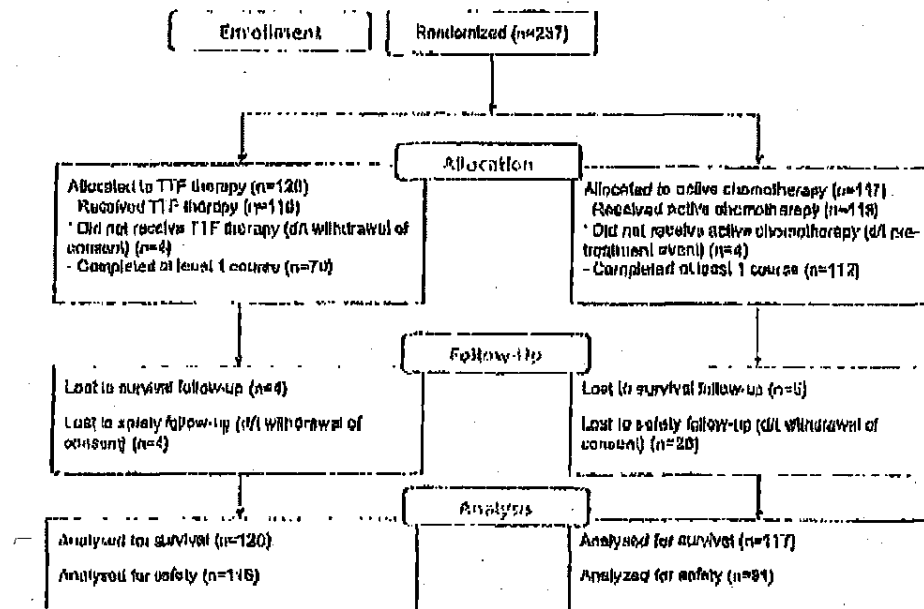
In the TTF group, 116 of 120 patients (97%) started treatment and 93 patients (78%) completed 4 weeks of therapy (1 cycle). Twenty-seven patients discontinued treatment early, often within a few days, due to non-compliance or inability to handle the device (trial flow

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diagram). Four patients had pre-treatment events related to the progressive nature of their disease and never started therapy with the device. In the TTF patients who started treatment (116 patients) mean compliance was measured by downloading a log file from the device, which recorded the actual time TTF therapy was delivered. Median compliance was 86 per cent (range 41–98%) of the time in each treatment month, translating into a mean use of 20.6 h per day.

apy (6.6 versus 6.0 months, respectively). One-year survival proportion was 20% in both groups, the 2- and 3-year survival rates survival rates were 8% (95% CI 4, 13) and 4% (95% CI 1, 8) versus 5% (95% CI 3, 10) and 1% (95% CI 0, 3), for TTF versus active control, respectively (Fig. 1A). The hazard ratio for death was 0.86 (95% CI 0.66, 1.12) in favour of NovoTTF ($p = 0.27$). Adjusting for baseline characteristics using a Cox proportional hazards model did not substantially

trial flow diagram



In the active control group, 113 of 117 patients (97%) started chemotherapy and all but 1 patient completed one full treatment course of the chosen chemotherapy. In four patients disease related adverse events and tumour progression prevented the initiation of the planned chemotherapy, they only received supportive care (hospice care). Twenty-one patients randomized to the control group decided not to return to the investigational site for treatment, thus details on disease progression and toxicity are not available. Most of patients received single agent or a combination chemotherapy regimen containing bevacizumab (31%), or irinotecan (31%), followed by nitrosoureas (25%), carboplatin (13%), temozolomide (11%) or various other agents (5%; Supplementary Table 1).

3.3. Survival, progression and radiological response

At a median follow up of 39 months, 220 patients had died (93%). Median survival was marginally higher in the TTF group compared to active control chemother-

apy after the results. In the active chemotherapy control arm of the trial, survival was not significantly affected by the choice of chemotherapy (Cox proportional hazards test; $p = 0.66$).

More objective radiological responses (partial and complete responses) were seen in the TTF group than in the active control chemotherapy group (14 versus 7, respectively), translating into a response rate in evaluated patients of 14.0% (95% CI 7.9–22.4%) versus 9.6% (95% CI 3.9–18.3%), respectively (chi squared $p = 0.19$). All three complete responses were observed in the TTF group. Two exemplary partial responses from TTF are shown in Fig. 3.

The trial had been designed for superiority. Since the control group in the trial is an active chemotherapy control which showed similar efficacy to that seen in previous trials and the device was used as monotherapy it is reasonable to analyse the results also in the context of a non-inferiority analysis. The HR for death in the TTF group compared to the active control chemotherapy group was below 1.0 (0.86; 95% CI 0.66–1.12), indi-

Please cite this article in press as: Stupp R, et al., NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality. *Eur J Cancer* (2012), <https://doi.org/10.1016/j.ejca.2012.04.011>

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Table 1
Baseline characteristics.

| Characteristics | Tumour Treatment Fields (TTF) (n = 120) # pts (%) | Active control (n = 117) # pts (%) |
|----------------------------------------------------------|------------------------------------------------------|---------------------------------------|
| Age, median (range) | 54 years (24-80) | 54 years (29-74) |
| Gender | | |
| Male | 92 (77) | 73 (62) |
| Female | 28 (23) | 44 (38) |
| Histology | | |
| Oligoblastoma | 100% | 100% |
| Prior lower grade glioma | 10 (8) | 9 (8) |
| Karnofsky performance status, median (range) | 80% (50-100) | 80% (50-100) |
| Steroid use at enrollment | | |
| Yes | 95 (40) | 62 (33) |
| No | 95 (46) | 49 (42) |
| Unknown | 10 (8) | 6 (5) |
| Largest tumour diameter at randomisation, median (range) | 6.1 cm (0-15.2) | 5.5 cm (0-16.2) |
| Interval from initial glioma diagnosis, median (range) | 11.8 months (3.2-99.3) | 11.4 months (2.9-77.1) |
| Prior therapy | | |
| 1st recurrence | 11 (9) | 17 (15) |
| 2nd recurrence | 58 (48) | 54 (46) |
| 3rd or greater recurrence | 51 (43) | 46 (39) |
| Surgery | | |
| Debulking before enrollment | 33 (28) | 29 (25) |
| Debulking at any stage | 95 (79) | 99 (85) |
| Biopsy only | 25 (21) | 18 (15) |
| Radiotherapy | | |
| With concomitant temozolomide | 100% | 100% |
| No concomitant temozolomide | 103 (86) | 96 (82) |
| Unknown | 15 (13) | 20 (17) |
| Prior adjuvant (maintenance) temozolomide | 2 (1) | 1 (1) |
| Median no of cycles | 100 (83) | 89 (76) |
| Prior bevacizumab | 4 (0-19) | 3 (0-27) |
| | 23 (19) | 31 (18) |

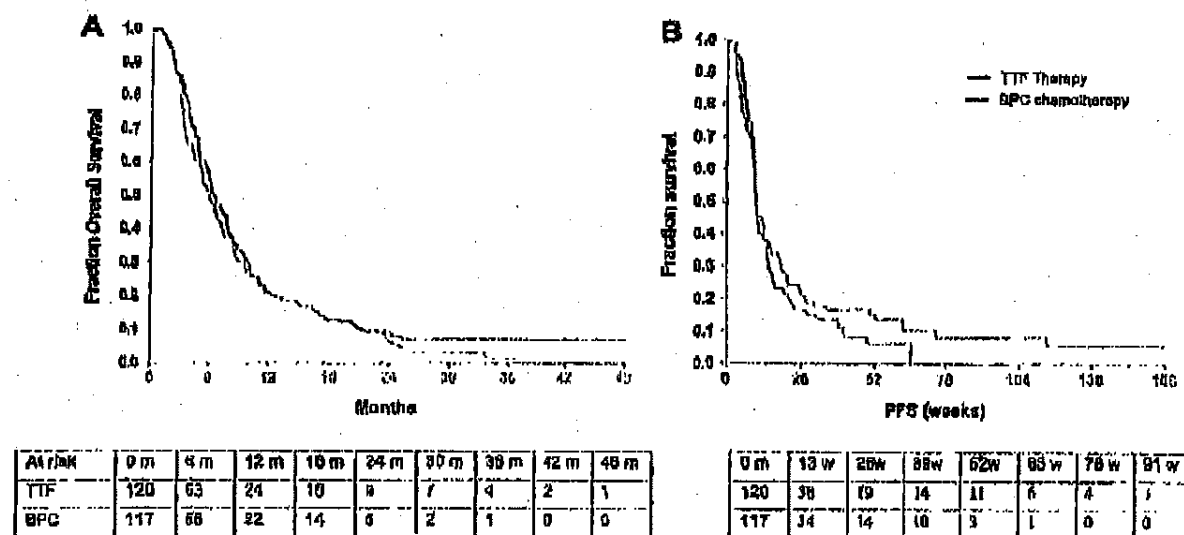


Fig. 2. Overall survival (A) and progression free survival (B) Kaplan-Meier curves.

noting that TTF may be at least equivalent to active chemotherapy.

PFS showed a similar trend in favour of TTF patients as seen for OS (Fig. 1B). Median PFS was 2.2 and

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2.1 months for TTF and active control groups, respectively (Fig. 2; HR 0.81, 95% CI 0.60–1.09; log rank $p = 0.16$). PFS6 was 21.4 per cent (95% CI 13.5–29.3) in the TTF group and 15.1 per cent (95% CI 7.8–22.3) in the active control group (chi squared $p = 0.13$).

3.4. Safety and toxicity

As expected from the mechanism of action of TTF therapy and the fact that its delivery is localised to the head, the typical systemic side-effects of chemotherapies were not observed in the TTF treated patients. Mild to moderate (grade 1 and 2) contact dermatitis on the scalp beneath the transducer arrays occurred in 16% of TTF patients (Fig. 1B). This condition was easily treated with topical corticosteroids, resolved completely after treatment, was stopped and did not require substantial treatment breaks.

Patients receiving active control chemotherapy experienced toxicity related to pharmacologic mechanism of the agents used. A list of grade 2–4 adverse events by organ system and adverse event terms seen in more than 2% of patients in either group is presented in Table 2. As expected, there were significantly more gastrointestinal, haematological and infectious adverse events seen in the chemotherapy group than in the TTF group. Severe

(grades 3 and 4) toxicity was observed in only 3% of patients.

3.5. Quality of life

Longitudinal Quality of Life (QOL) could be analysed in the patients who remained on study therapy for ≥ 3 months and for whom QoL data were available (63 patients, 27%). In the domains of global health and social functioning no meaningful differences between chemotherapy and TTF were observed. However, cognitive and emotional functioning favoured TTF. Physical functioning may be slightly worse with TTF, while role functioning favoured TTF (Fig. 4A). Symptom scale analysis is in accordance to treatment-associated toxicity; appetite loss, diarrhoea, constipation, nausea and vomiting were directly related to the chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the TTF treatment group (Fig. 4B).

3.6. Treatment after progression

In order to rule out the effect of subsequent treatments on the OS results reported above, we compared the number and type of post-progression treatments patients received after failing the trial therapy. Due to

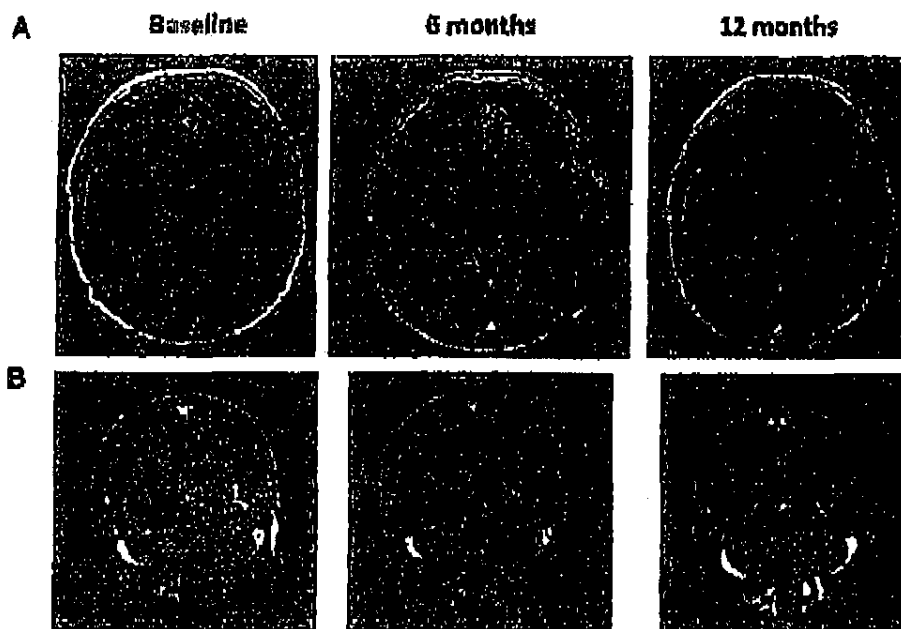


Fig. 3. Exemplary T1 weighted magnetic resonance imaging (MRI) images with gadolinium from two Tumour Treatment Fields (TTF) patients with partial response to therapy. (A) A 48 years old male with prior grade II astrocytoma which transformed to glioblastoma (based on tissue biopsy). The subject progressed 7 months after receiving chemoradiotherapy, and subsequently responded to TTF therapy (partial response at 12 months) and remained stable for an additional 36+ months on TTF. (B) A 55 years old male with primary glioblastoma who recurred for the third time after receiving chemoradiotherapy, adjuvant temozolomide (2 cycles), bevacizumab with irinotecan (3 months) and etoposide with sorafenib (one cycle). The subject had a partial response to TTF therapy after 4 months of treatment and remained stable for an additional 8 months while on TTF.

Please cite this article in press as: Stupp R, et al. NovoTTF-100A versus physician choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality. *Eur J Cancer* (2012). <http://dx.doi.org/10.1016/j.ejca.2012.04.011>

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Table 2
Treatment-emergent adverse events ≥ grade 2 by body system.

| System | Adverse event term | Tumour Treatment Fields (TTF) (n = 116) % (% gr. 3 + 4) | Active control (n = 91) % (% gr. 3 + 4) |
|-----------------------------------|-----------------------|------------------------------------------------------------|--------------------------------------------|
| Haematological | | 3 (0) | 17 (4) |
| | Leucopenia | 0 (0) | 5 (1) |
| | Neutropenia | 0 (0) | 2 (1) |
| | Thrombocytopenia | 1 (1) ^a | 7 (2) |
| Gastrointestinal disorders | | 4 (1) | 17 (3) |
| | Abdominal pain | 0 (0) | 3 (0) |
| | Diarrhoea | 0 (0) | 5 (3) |
| | Nausea/vomiting | 2 (0) | 7 (0) |
| General deterioration and malaise | | 5 (1) | 6 (1) |
| | Infections | 4 (0) | 8 (1) |
| Skin rash (transducer arrays) | | 2 (0) | 0 (0) |
| Metabolic and nutrition disorders | | 4 (1) | 6 (3) |
| Musculoskeletal disorders | | 2 (0) | 5 (0) |
| Nervous system disorders | | 30 (7) | 28 (7) |
| | Brain oedema | 0 (0) | 2 (0) |
| | Cognitive disorder | 2 (1) | 2 (2) |
| | Convulsion | 7 (2) | 5 (2) |
| | Dysphasia | 2 (0) | 1 (0) |
| | Headache | 8 (1) | 6 (0) |
| | Hemianopsia | 1 (0) | 3 (1) |
| | Hemiparesis | 3 (1) | 2 (1) |
| | Neuropathy peripheral | 2 (0) | 2 (0) |
| Psychiatric disorders | | 5 (0) | 4 (0) |
| Renal and urinary disorders | | 3 (1) | 3 (0) |
| Respiratory disorders | | 1 (0) | 1 (1) |
| Vascular disorders | | 3 (1) | 4 (3) |
| | Pulmonary embolism | 1 (1) | 2 (2) |
| | Hypertension | 1 (0) | 1 (1) |
| | Deep vein thrombosis | 1 (0) | 1 (0) |

^a Thrombocytopenia from prior chemotherapy, normalized subsequently.

the very advanced stage they were recruited to the study (most patients were at their second or subsequent recurrence), only 5.8% of the TTF-treated patients and 10.3% of the chemotherapy-treated patients received subsequent salvage antitumour therapy (chi square $p = 0.24$) (mainly bevacizumab, irinotecan, nitrosoureas and temozolomide). The majority of patients received only supportive care once tumour progression developed.

4. Discussion

Tumour treatment with alternating electrical fields that interfere with the metaphase to anaphase transition in dividing tumour cells is an entirely novel cancer treatment modality. We report the first prospective, randomised, controlled study using this new treatment modality in the most aggressive primary brain tumour. Although glioblastoma diffusely infiltrates the brain, it almost never metastasises and is thus amenable to a loco-regional therapy.

Prognosis of patients with recurrent glioblastoma is poor, and chemotherapy is usually recommended. Depending on prior treatments and treatment centre expertise, variable chemotherapy agents alone or in combination are commonly prescribed. Our randomised trial compared this standard chemotherapy per local

practice (active treatment control group) with TTF in a prospective, multicentre phase III trial. Although the trial did not reach its primary end-point of improved survival compared to active chemotherapy, this new minimally invasive and chemotherapy-free local treatment modality demonstrated a statistically non-significant increased response rate (14 versus 9.6%, $p = 0.19$), an improved PFS6 rate (21% versus 15%, $p = 0.13$), and a trend towards reduction of the risk of death (hazard ratio 0.86, 95% CI 0.66–1.12, $p = 0.27$), as well as sustained improvement in QoL.

These results cannot be explained by subsequent salvage chemotherapy, as few patients received additional therapy after failure of protocol treatment. Importantly, the majority of our patients were recruited to the trial at an advanced stage of the disease, after failure of two or more chemotherapy agents, while other trials in recurrent glioblastoma usually only enrol patients at first recurrence. It is also notable that 20% of patients had failed prior bevacizumab therapy, a population that usually fares poorly with most subsequent treatments.

One limitation of the study was the absence of a placebo or treatment-free control arm. In the setting of advanced disease and chemotherapy considered indicated and effective, such a control would hardly have been acceptable to patients and physicians alike. Fur-

Website that reports in press: Stupp R, et al. Novel TTF/TTA versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality. *J Clin Oncol* 2012;30(12):1311-1319. doi:10.1200/JCO.2012.01.0117

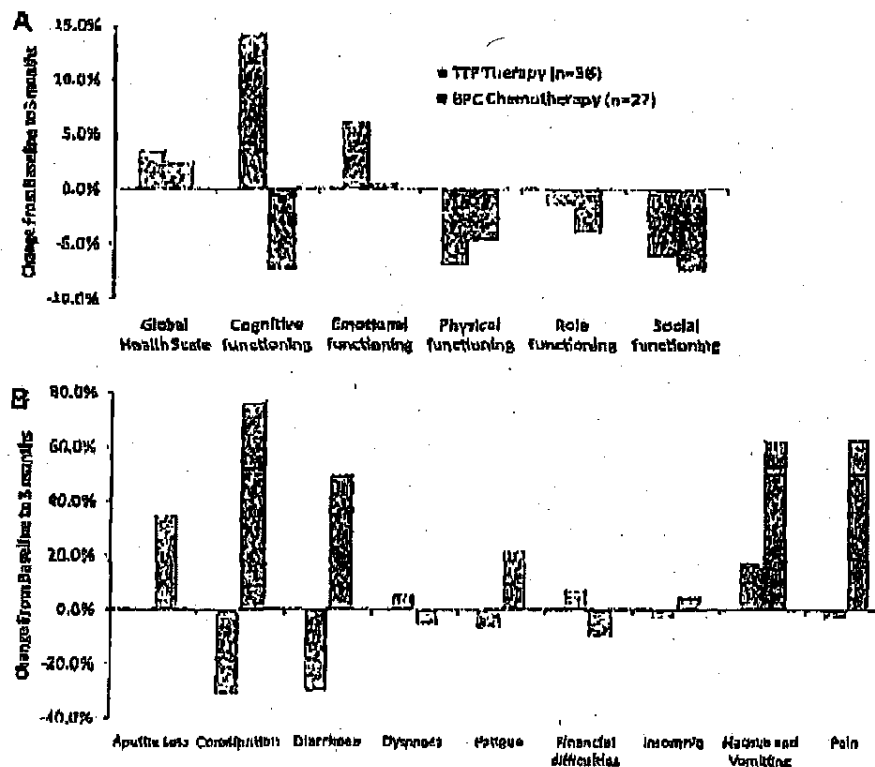


Fig. 4. QLQ C30 longitudinal change from base to 3 months. (A) General functional scales (an increase in percentage corresponds to an increase in QOL). (B) Symptom scales (an increase in percentage corresponds to a decrease in QOL).

thermore, chemotherapy with lomustine has shown superior efficacy versus investigational treatments in two recent randomised trials. And based on high response rates and prolonged survival compared to historical controls bevacizumab has received accelerated Food and Drug Administration (FDA) approval. Furthermore, the observation of objective responses in 14 patients with NovoTTF alone (median time since end of prior RT 7 months, thus unlikely to be all pseudoprogression) strongly suggests singular activity of this device.

Another limitation is the somewhat heterogeneous patient population, with patients included after progression of one or several lines of prior chemotherapy. This underscores the demand from patients for further treatments, even when the expected benefit of a 2 months prolongation in PFS may appear modest. In the ongoing randomised phase III trial for newly diagnosed glioblastoma, only patients non-progressive after completion of chemoradiation are eligible (Novocure EF-14, www.clinicaltrials.gov, NCT#00916409).

As expected with a local treatment, toxicity was limited to skin irritation from transducer arrays (Fig. 1B). After proper instructions, most patients became independent in handling this device and replacing transducer arrays, allowing them to be ambulatory and even going to work. Despite the inconvenience of carrying and

using the device almost permanently, compliance was high and patients reported improvement in QoL in the absence of chemotherapy related toxicities.

In vitro and animal experiments suggest enhanced effect when TTF is combined with chemotherapy.^{25,32} We therefore initiated a subsequent randomised phase III trial currently enrolling newly diagnosed glioblastoma patients after completion of standard radio-chemotherapy, parallel to starting the adjuvant or maintenance temozolomide chemotherapy. Patients randomised to the experimental arm will receive TTF in addition to maintenance temozolomide (www.clinicaltrials.gov, NCT#00916409).

Based on the result of this trial TTF therapy has recently been approved in the US and Europe for the treatment of recurrent glioblastoma (www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm251669.htm).

The universal anti-cancer effect of TTF may be applicable to other solid tumour types, alone or in combination with chemotherapy. In particular, in a situation of morbidity induced by a heavy local tumour burden, and in conditions where further radiotherapy is not an option, this non-invasive treatment may allow for a clinical benefit and will substantially expand our treatment armamentarium.

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Conflict of interest statement

Eilon Kirson and Uri Weinberg are employees of Novocure Ltd., and have stock options in the company.

Herwig Kestron has received honoraria from Novocure Ltd.

Yoram Palti is the inventor of the Novo-TTP principle. He received consulting honoraria and travel support by Novocure Ltd.

Nina Paleologos has served on advisory boards and speakers bureau to Genentech, Merck & Co (previously Schering-Plough).

Susan Patullo has received research grants from Novocure, NTI Pharma, Eisai, Immunocellular and Parexel, and honoraria for lectures from Merck & Co (previously Schering-Plough).

Zvi Ram is a board member for Novocure, and received consultancy honoraria.

Jeffrey Raizer has received research support from Novocure Ltd., performed consultancy for Merck and Genentech/Roche, and lectures on behalf of Merck & Co, Genentech and Enzo.

David Schiff has performed consultancy for Genentech and Tan Pharmaceuticals.

Andrew Sloan has provided consultancy to Genentech/Roche, Real Bio Inc., NanSiber Solutions, Surgical Theatre and Montecris Medical Inc.

Roger Stupp has served on scientific advisory boards for Merck-Serono, Roche, Actelion, MDxHealth (previously OncoMethylomeScience) and Merck and Co (previously Schering-Plough).

Manfred Westphal has received consultancy honoraria from Roche, OncoScience and Ark Therapeutics.

Brio T. Wong has received research support from Novocure Ltd.

The following authors declare no potential conflict of interest: Jeffrey Bruce, Lawrence Chin, Rees Cosgrove, Vladimir Dabaly, Herbert Engelhard, Philip Guthi, Volkmar Hentschke, Silvia Hofer, Andrew Kanner, Lara Kunscher, Joseph Landolfi, Frank Linherman, Marc Malkin, Maximilian Mohdorn, Franz Payer, Martin Smeyka, David Steinberg, J. Lee Villano, and Robert Weil.

Acknowledgements

We are indebted to the patients and their families for agreeing to participate in this trial. We thank all the local site co-investigators, and trial coordinators at the participating centres for their hard and diligent work, as well as the nurses at the trial site and Novocure technicians for the great patient care provided. We express our special thanks to Martine Lionnet, Francois Ducray, Stéphanie Cartelat-Carel, Marie Fasol, Valerie Bleig, Mike Ambroggi, Shawn Andrews, Yoram Wasserman and Zoya Gurvich.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ejca.2012.04.011>.

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NovoTTF-100A: a new treatment modality for recurrent glioblastoma

Expert Rev. Neurother. doi:10.1586/ERN.12.80 (2012) (Epub ahead of print)

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NovoTTF-100A (Novocure Inc., Haifa, Israel) is a first-of-a-kind device approved by the US FDA for the treatment of recurrent glioblastoma. It works by emitting a low-intensity, intermediate-frequency (200 kHz), alternating electric field administered via insulated transducer arrays applied onto the scalp. The electric field penetrates the brain and inhibits the growth and proliferation of glioblastoma by interfering with tumor cell mitosis at anaphase. Results from a Phase III clinical trial indicate that the efficacy of NovoTTF-100A is equivalent to standard-of-care chemotherapy. The side effect profile favors device-treated patients, obviating typical toxicities associated with chemotherapy or targeted drugs, and results in improvements in their quality of life. NovoTTF-100A is a new modality of cancer treatment that offers equivalent efficacy, but less toxicity, to recurrent glioblastoma patients when compared with existing treatments.

Keywords: chemotherapy • electric field • glioblastoma • NovoTTF-100A • tumor-treating field

Overview of the market

Despite continuing research in drug treatments for glioblastomas, median patient survival remains a dismal 14.6 months from the time of initial diagnosis using combined radiation and chemotherapy [1]. Fewer than 10% of patients survive to the 5-year time point [2]. At the time of glioblastoma recurrence or progression, the overall survival (OS) of patients is even worse – typically 6 months or less [3]. The only US FDA-approved medical treatment for recurrence is bevacizumab, but this drug has never been tested in a Phase III clinical trial. Current salvage treatment with bevacizumab prolongs only the progression-free survival (PFS), but not OS, and the tumor invariably progresses in an infiltrative pattern, causing neurological deficits and eventual death [4,5]. Both bevacizumab and cytotoxic chemotherapies have serious side effects that include hemorrhage, thromboembolism, infection, hypertensive crisis, renal failure, diarrhea, nausea and vomiting [4–6]. Therefore, there is a great unmet need for novel therapies that have new mechanisms of action against glioblastoma and a more favorable toxicity profile.

Introduction

NovoTTF-100A (Novocure Inc., Haifa, Israel) is a novel class of therapeutic device being used

for the treatment of recurrent glioblastomas. It works by emitting low-intensity, intermediate-frequency (200 kHz), alternating electric fields administered by insulated transducer arrays to inhibit the growth and proliferation of intracranial glioblastomas [7]. This device, which consists of the transducer arrays, electric field generator (set at a frequency of 200 kHz) and battery (Figure 1), was approved for use by the FDA on 8 April 2011 [8]. This review summarizes its mechanisms of action, Phase III efficacy and safety data, and current use in clinical practice.

Mechanism of action

NovoTTF-100A exerts its anti-tumor effect on glioblastoma cells by interfering with mitosis at anaphase. In synchronized cell culture, such a tumor-treating electric field (TTField) first disrupted cytokinesis and then impaired chromosome separation from the metaphase plates [9]. Biochemical assays also confirmed that these cells had already transitioned from metaphase to anaphase [10]. Immunofluorescence of treated cells demonstrated lagging chromosomes, dispersion of chromosomes, chromosomal decondensation in the absence of cytokinesis, and asymmetric chromosome segregation [9,9]. Exposed cells showed no p53 induction, suggesting that cell death was mediated via a p53-independent

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Figure 1. The NovoTTF-100A device setup. Left panel: The NovoTTF-100A device. Right panel: Two opposing pairs of transducer arrays (A) are applied to the scalp and the cables are linked to the connection box (B). The connection box is then attached to the electric field generator (C), which is connected to a power supply (D). The entire set up weighs approximately 7 lbs.

mechanism [8]. Furthermore, susceptibility to TTFeld is cell type dependent. Both glioma cells from rats (R-98) and humans (U87 and U118) have a significantly decreased growth rate when exposed to TTFeld [9]. The best result appears to occur at an intensity of 2.25 V/cm and a frequency of 200 kHz [9]. Taken together, TTFeld represents a new modality of anticancer treatment via a mechanism that differs from conventional radiotherapy, cytotoxic chemotherapies or targeted kinase inhibitors. However, additional research is needed to determine the effect on postmitotic neurons and glia, as well as dividing progenitor cells, within the brain.

Clinical efficacy

NovoTTF-100A underwent initial testing in a pilot trial of ten patients with recurrent glioblastoma [7]. The results showed that the median time to disease progression was 26.1 weeks (range: 3.0–124.0 weeks), the PFS at 6 months (PFS6) was 50% (95% CI: 23–77%), and the median OS was 62.2 weeks (range: 20.3–124.0 weeks) [1]. There were two durable responses, including two patients with complete and partial responses lasting 43.3+ weeks and 30.3+ weeks, respectively [7]. These preliminary data compared favorably to benchmark outcomes from conventional cytotoxic chemotherapies, which had a response rate of 9%, PFS6 of 15%, median PFS of 9.0 weeks, and a median OS of 25.0 weeks (95% CI: 21–28 weeks) [3].

NovoTTF-100A was subsequently compared to best standard of care (BSC) chemotherapy for recurrent glioblastoma after initial temozolomide chemoradiation in a prospective, randomized, open-label Phase III clinical trial. Among the 26 centers in the USA and Europe, 237 individuals were randomized to NovoTTF-100A alone (120 subjects) or BSC (117 subjects) [10,11]. The primary end point was OS and secondary end points included PRS, PFS6, 1-year survival rate, objective radiological response, quality of life and safety. All analyses were performed on the intent-to-treat population, and Kaplan-Meier OS and PFS were computed from the time of randomization until event or censoring at last

follow-up. The trial was powered at 80%, with a significance of $p \leq 0.05$ and a hazard ratio (HR) for death of ≤ 0.67 . The median age, Karnofsky Performance Score and other clinical characteristics were balanced between the two cohorts, with the exception of slightly larger tumor size in the NovoTTF-100A group versus the BSC group, at a median size of 6.1 cm (range: 0.0–15.2 cm) and 5.5 cm (range: 0.0–16.2 cm), respectively (Table 1) [10,11]. BSC chemotherapies chosen by the treating physician included single-agent or combination irinotecan (31%), bevacizumab (31%), BCNU/CCNU (25%), carboplatin (13%), temozolomide (11%), combination procarbazine, CCNU and vincristine (9%), etoposide (3%), imatinib (2%), hydroxyurea (1%), or nothing (3%) [10,11]. In the intent-

to-treat population, the median OS was 28.6 versus 26.0 weeks (HR: 0.86; 95% CI: 0.66–1.12), the median PFS was 9.3 versus 9.1 weeks (HR: 0.84, 95% CI: 0.64–1.13), and the median PFS6 was 21 versus 15% for NovoTTF-100A and BSC chemotherapy, respectively (Figure 1) [10,11]. The data indicate that NovoTTF-100A has an equivalent efficacy when compared to salvage cytotoxic chemotherapies and targeted drugs for recurrent glioblastoma. Interestingly, patients who failed bevacizumab and then enrolled to receive NovoTTF-100A ($n = 23$) had a significantly longer survival than those who received BSC chemotherapy ($n = 21$), at 19.1 versus 13.4 weeks ($p < 0.02$), respectively [12].

Safety & tolerability

The side effect profile favors NovoTTF-100A treatment significantly more than BSC. Notably, there were only 3 versus 17% hematological toxicities, 4 versus 17% gastrointestinal side effects, and 4 versus 8% infections at grade 3 or 4 severity in the NovoTTF-100A versus BSC cohorts, respectively [10,11]. Other systemic toxicities were well-balanced between the two groups. However, scalp irritation from transducer array placement did occur at a higher frequency, with 17% grade 1 and 2 skin rash in the NovoTTF-100A subjects when compared with 0% in those treated with BSC chemotherapy [10,11]. However, none of the device-treated patients experienced skin toxicity higher than grade 2. Additional self-reported quality-of-life analysis by EORTC QLQ C-30 showed positive scores from NovoTTF-100A usage due to improved cognitive function, decreased constipation and diarrhea complications, as well as absence of pain [11,13].

Use in practice

Certain medical conditions are contraindicated in NovoTTF-100A usage and may pose unknown risks to patients. First, it is inadvisable to prescribe this device to patients with active implanted medical devices, such as cardiac pacemakers, defibrillators, deep-brain stimulators, vagus nerve stimulators and

doi:10.1586/BRN.12.02

Expert Rev Neurother. 12(6). (2012)

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Table 1. Baseline characteristics of subjects enrolled in the Phase III NovoTTF-100A trial for recurrent glioblastoma.

| | 54 (24-80) years | 54 (29-74) years |
|---------------------------------------------------------|------------------------|------------------------|
| Age, median (range) | | |
| Gender: | | |
| -- Male | 92 (77%) | 73 (62%) |
| -- Female | 28 (23%) | 44 (38%) |
| Histology: | | |
| -- Primary glioblastoma | 110 (92%) | 108 (92%) |
| -- Secondary glioblastoma | 10 (8%) | 9 (8%) |
| Karnofsky performance status, median (range) | 80 (50-100) | 80 (50-100) |
| Corticosteroid use at the time of enrollment: | | |
| -- Yes | 55 (46%) | 62 (53%) |
| -- No | 55 (46%) | 49 (42%) |
| -- Unknown | 10 (8%) | 0 (0%) |
| Maximum tumor diameter at randomization, median (range) | 6.1 (0.0-15.2) cm | 6.5 (0.0-16.2) cm |
| Time from initial glioma diagnosis, median (range) | 11.8 (3.2-99.3) months | 11.4 (2.9-77.1) months |
| First recurrence | 11 (9%) | 17 (15%) |
| Second recurrence | 58 (48%) | 54 (46%) |
| Third or greater recurrence | 51 (43%) | 46 (39%) |
| Surgery: | | |
| -- Debulking surgery prior to enrollment | 33 (28%) | 29 (25%) |
| -- Debulking at any stage | 95 (79%) | 99 (85%) |
| -- Biopsy only | 25 (21%) | 18 (15%) |
| Radiotherapy: | 120 (100%) | 117 (100%) |
| -- Radiotherapy with concomitant temozolomide | 103 (85%) | 96 (82%) |
| -- Radiotherapy without concomitant temozolomide | 15 (13%) | 20 (17%) |
| -- Unknown | 2 (1%) | 1 (1%) |
| Prior adjuvant (maintenance) temozolomide | 100 (83%) | 89 (76%) |
| Median number of cycles | 4 (0-19) | 3 (0-27) |
| Prior bevacizumab use | 23 (19%) | 21 (18%) |
| Data taken from (1). | | |

programmable ventriculoperitoneal shunts. These devices may cause reciprocal electromagnetic interference, induction or both, and the extent of this risk is unknown. Second, patients with major skull defects cannot receive this treatment. For example, those with a missing section of the calvarium may experience elevated electric field strength on the brain. However, those with healed burr holes and craniotomy sutures can receive this treatment without complications. Third, metals within the brain are also contraindicated because NovoTTF-100A has not been tested in patients with bullet fragments or aneurysm clips in their head. Last, those with hypersensitivity to hydrogel, which is used as a

conductive interface between the transducer array disks and the scalp, may not be able to receive this treatment.

Pre-treatment evaluation consists of baseline history, physical examination (including evaluation of skin integrity on the scalp), blood work and gadolinium-enhanced head MRI. The MRI images are used to construct a mapping diagram for placement of the transducer arrays. Typically, there are two pairs of opposing arrays, which are separately color coded (Figure 1). The wires of the arrays are then connected to the electric field generator and power supply (Figure 1). The patient's hair is then shaved off with an electric shaver instead of a razor in order to avoid superficial

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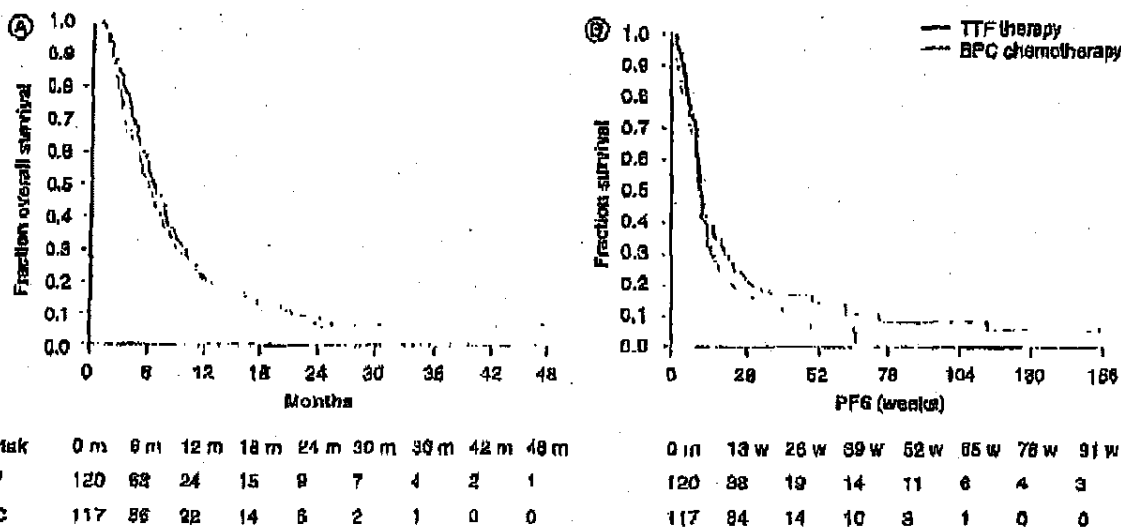


Figure 2. Data from a Phase III NovoTTF-100A trial for recurrent glioblastoma. (A) Kaplan-Meier curves showing equivalent overall survival between the NovoTTF-100A therapy group and the BPC active control. (B) Kaplan-Meier progression-free survival curves showing a greater number of subjects with disease stabilization in the NovoTTF-100A-treated group than BPC active control; four subjects without disease progression at 78 weeks and three at 91 weeks versus none in the control.

BPC: Best physician choice; m: Months; PFS: Progression-free survival; w: Weeks.
Reproduced with permission from [11].

cure. The scalp is then cleaned with alcohol prior to application of the arrays. This procedure typically requires the help of another individual and it is necessary to bring a family member or assistant to learn array placement and operation of the NovoTTF-100A device. Follow-up clinic visits are scheduled monthly in the first 3 months and then every 2 months thereafter. Gadolinium-enhanced head MRI is performed once every 2 months for monitoring the status of glioblastoma during treatment.

The efficacy of NovoTTF-100A on brain tumors other than glioblastoma is unknown. However, other gliomas may respond to the same frequency (200 kHz) emitted by the NovoTTF-100A device, based on published preclinical data. However, it is still unknown whether or not TTF field at 200 kHz would be effective in controlling metastatic brain tumors because the optimal frequency for specific metastasis may be different. For example, in preclinical cell culture melanoma was most sensitive at a frequency of 120 kHz [5].

Regulatory affairs

NovoTTF-100A is currently approved by the FDA and the EMA for the treatment of recurrent or progressive glioblastomas.

Conclusion

NovoTTF-100A is a novel therapy for the treatment of recurrent glioblastoma. It emits TTF field that interferes with dividing tumor cells at anaphase. The clinical trial results indicate that it has comparable efficacy and less toxicity when compared to conventional drug treatments in the recurrence setting.

Expert commentary

The Phase III clinical trial demonstrated comparable, but not superior, efficacy when compared to conventional drug treatment. This result is likely to be influenced by a number of factors. First, the population of patients with recurrent glioblastoma has neurological deterioration and death within a shorter time than those with newly diagnosed disease. As a result, these patients may deteriorate early and therefore their tumors may not receive enough exposure to NovoTTF-100A treatment. Unlike conventional cytotoxic chemotherapies that have a biological effect lasting the entire duration of the treatment cycle (typically 4–6 weeks), the TTF field needs to be applied continuously otherwise the anti-tumor effect would disappear as soon as the generator is switched off. Consistent with this reasoning, the per-protocol analysis of the Phase III trial data, in which patients who received less than 4 weeks of NovoTTF-100A treatment were removed from analysis, showed that NovoTTF-100A offered a statistically significant survival advantage when compared to RSC chemotherapy. Second, compared to newly diagnosed glioblastomas, recurrent glioblastomas have additional genetic alterations making them more resistant to treatment [23,19]. Therefore, NovoTTF-100A may have a greater benefit to newly diagnosed patients than those with recurrent disease. A Phase III clinical trial is currently underway investigating the efficacy of NovoTTF-100A with temozolomide chemoradiation compared to standard temozolomide chemoradiation for newly diagnosed glioblastoma. Last, NovoTTF-100A does not appear to have overlapping toxicity with conventional drug treatments [11,11]. Therefore,

doi:10.1586/RRM.12.60

Report of a Reviewer (2013). (2013)

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combining it with cytotoxic chemotherapies or targeted agents can potentially result in increased efficacy and without added toxicity. The pivotal Phase III trial did include patients after failure of temozolomide with carmustine implant (Gliadel wafers) [1]. However, for patients who have undergone wafer implantation, it would be best to withhold the use of NovoTTF-100A until complete dissolution of the wafer, which typically occurs in 4 weeks. However, more preclinical data are needed in order to find the optimal NovoTTF-100A and drug combinations before they can be applied in a clinical trial setting.

Five-year view

In the next 5 years, more preclinical studies are needed in order to determine the mechanisms of TTField's action on tumor cells. The results would most likely offer ideas for investigator-initiated clinical research that would help to maximize the efficacy of NovoTTF-100A against glioblastomas. This will most likely

be accomplished by the addition of drugs that have synergistic or additive activities. A logical combination treatment would include NovoTTF-100A and bevacizumab because these two therapies do not have overlapping toxicity and both are approved by the FDA for the treatment of recurrent glioblastomas. Furthermore, the device could also be used to treat patients with metastatic brain tumors. However, more preclinical and clinical research is needed to support its use in these patients, as well as the specific type of metastatic brain tumor that shows sensitivity to TTField.

Financial & competing interests disclosure

Dr ET Wong receives research support from NeuroCyte, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- NovoTTF-100A (Novocure Inc., Haifa, Israel) emits a low-intensity, intermediate-frequency (200 kHz) alternating electric field that treats recurrent glioblastomas.
- NovoTTF-100A exerts its anti-tumor effect on glioblastoma cells by interfering with mitosis at anaphase.
- NovoTTF-100A treatment offers comparable efficacy when compared to conventional drug treatments, including bevacizumab, for recurrent glioblastoma.
- The toxicity profile favors NovoTTF-100A over conventional drug treatments.

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By Phillip H. Gutin, MD, and Eric T. Wong, MD

Overview: Tumor treating fields (TTF) therapy is a novel antimitotic, electric field-based treatment for cancer. This nonchemical, nonablative treatment is unlike any of the established cancer treatment modalities, such as surgery, radiation, and chemotherapy. Recently, it has entered clinical use after a decade of intensive translational research. TTF therapy is delivered to patients by a portable, battery-operated, medical device using noninvasive transducer arrays placed on the skin surface surrounding the treated tumor. TTF therapy is

now a U.S. Food and Drug Administration (FDA)-approved treatment for patients with recurrent glioblastoma (GBM) who have exhausted surgical and radiation treatments. This article will introduce the basic science behind TTF therapy, its mechanism of action, the preclinical findings that led to its clinical testing, and the clinical safety and efficacy data available to date, as well as offer future research directions on this novel treatment modality for cancer.

THE DEFINITION of the electric field is attributed to Michael Faraday in the 1820s and was later formulated by James Clerk Maxwell in his electromagnetism theory in 1860.¹ It is a field of electric forces that surround a source charge. When a test charge is placed within an electric field, a force acts on it. Negative charges attract positive charges, while similar signed charges repel each other. As seen in Fig. 1A, an electric field surrounding a source charge can be described using diverging lines of force. The closer the test charge is to the source charge, the closer the lines of force are to each other, which represents higher field intensity.

To understand the effects of electric fields within cells, it is important to introduce three definitions. First, electric fields can be uniform or nonuniform. A uniform electric field is represented by parallel lines of force (Fig. 1B). A nonuniform electric field is represented by converging or diverging lines of force (Fig. 1A and 1D). Second, an electric field can be a constant field or a time-varying field, resulting in electrostatic or electrodynamics phenomena, respectively. In a constant field, the source charges remain the same over time. A test charge will move in one direction within a constant electric field toward the oppositely charged source (Fig. 1B). In a time-varying or alternating electric field, the charge of the sources alternates over time (Fig. 1C). Third, the test charge can be an electric charge or an electric dipole (an element with a positive charge on one end and a negative charge on the opposite end). An electric charge will move back and forth, while a dipole will rotate within an alternating uniform electric field and align with the direction of the field. In a nonuniform converging electric field, both dipoles and charges move in the direction of the higher field intensity through a process known as dielectrophoresis (Fig. 1D).

Mechanism of Action of TTF Therapy

Over 100 years after Maxwell's original publication, Yoram Palti, MD, PhD, hypothesized that properly tuned alternating electric fields at physiological intensities (i.e., 1–3 V/cm) would disrupt the mitotic process of dividing cancer cells.^{2,3} Dr. Palti hypothesized and subsequently demonstrated *in vitro* that at frequencies between 100 and 300 kHz, alternating electric fields disrupt the formation of the mitotic spindle during metaphase and lead to dielectrophoretic movement of charged and/or polar molecules and organelles during anaphase and telophase, disrupting normal cytokinesis and leading to apoptosis.^{2,3} According to this model, the first mechanism of action is explained by the fact

that the tubulin subunits are one of the most polar molecules in the cell. These tubulin subunits align in the direction of the applied electric field (Fig. 2A), interfering with the normal polymerization of the mitotic spindle, which results in formation of abnormal mitotic figures *in vitro*.³ The second mechanism of action is explained by examining the change in shape of the electric field within a dividing cell from anaphase to telophase. When the cell division axis is aligned with the direction of the electric field, the field lines that enter the cell at one end converge at the cytokinetic furrow between the developing daughter cells and then diverge on the opposite side (Fig. 2B). This nonuniform electric field within the cell generates dielectrophoretic forces that act on polar and charged elements in the cell, pushing them toward the cytokinetic furrow leading to violent blebbing of the plasma membrane.³ This finding was also validated by researchers from Beth Israel Deaconess Medical Center and may be mediated by improper placement of the contractile elements that form the cytokinetic ring on anaphase entry.⁴

Preclinical Studies of the Antitumor Effects of TTF Therapy

Between 2004 and 2010, a series of publications and conference presentations addressed the issue of the applicability range of TTF therapy to different *in vitro* and *in vivo* cancer models either alone or in combination with standard chemotherapy.^{5,6} Tables 1 and 2 summarize the state-of-the-art preclinical research with TTF therapy. TTF therapy has been shown to effectively inhibit cancer cell growth in various cell lines *in vitro* (Table 1). This effect was clearly dose (field intensity) dependent in the range of 1 to 8 V/cm.⁹ The optimal frequency for the inhibitory effect of TTF therapy differed between cell types and was inversely related to cell size (Table 1; e.g., glioma cell cultures at 200 kHz¹⁰). In addition, based on the directional nature of TTF

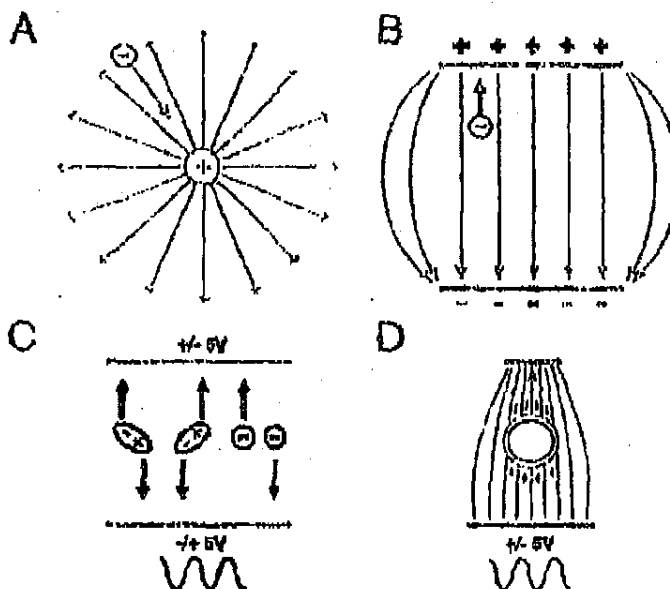
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1079-6116/18/3611-126

TTF THERAPY IN GLIOBLASTOMA

Fig. 1. Electric field theory. (A) Opposite charges attract. (B) A constant, uniform, electric field. (C) Charges and dipoles in a time-varying, uniform electric field. (D) A dipole in a time-varying, nonuniform electric field (dipolephoresis).



therapy, its antimitotic effect in cultures was enhanced by sequentially applying more than one field direction to the treated cells.⁴ The combination of TTF therapy with different chemotherapeutic agents has been shown to have at least additive if not synergistic effects.^{7,8} Specifically, the combination of TTF therapy with temozolomide in glioma cell lines was shown to be additive. Interestingly, in breast cancer cells, TTF therapy showed overt synergism with taxanes (e.g., paclitaxel), probably a result of the temporal

proximity of taxanes' effect in metaphase and TTF therapy's mitotic interference on cell entry into anaphase.⁹

TTF therapy has been tested in numerous *in vivo* cancer models (Table 2).^{8,9,10} Noninvasive application of TTF therapy to animals was performed using electrically insulated transducer arrays placed on the head or torso surrounding the region of the tumor. Inhibition of tumor growth was seen in each of these models when the correct frequency of TTF therapy was applied. Specifically, 200 kHz TTF therapy applied in two sequential and perpendicular field directions lead to significant ($p < 0.01$) inhibition of a syngeneic, orthotopic P-98 glioma in rats after 7 days of treatment.⁸ An additional syngeneic, orthotopic model of non-anast cell lung cancer in mice showed that 150 kHz TTF therapy significantly ($p < 0.01$) inhibited tumor growth within 7 days of treatment.^{9,11} Furthermore, the additive effect of TTF therapy with chemotherapy seen *in vitro* was recapitulated in different *in vivo* models.^{8,9} Finally, in a metastatic tumor model using a squamous carcinoma tumor implanted in the kidney capsule of rabbits, TTF therapy applied to the abdomen blocked metastatic spread of tumor from the kidney to the lungs.^{10,12}

Translating TTF Therapy into Clinical Use

Since TTF therapy is a physical antimitotic modality with no half-life, its application should be continuous. Kinetic modeling was used to predict the minimal treatment duration needed with TTF therapy.¹³ Based on those data, a minimal treatment course of 4 weeks was devised and implemented in clinical studies. *In vivo* animal experiments and pilot clinical data subsequently verified the 4-week minimal treatment duration.¹³ Such continuous delivery was made possible by the development of a portable, battery-operated, medical device that patients can use at home (NaveTTF-100A, Novanure, Kfar Saba, Israel). Finally, extensive toxicity studies of TTF therapy were performed in healthy

KEY POINTS

- Tumor treating fields (TTF) therapy is an emerging, low-toxicity treatment modality for solid tumors based on the delivery of antimitotic alternating electric fields to the tumor, which interferes with cytokinesis and microtubule assembly that eventually lead to cell death.
- As a monotherapy, TTF therapy is at least as effective as currently available active chemotherapy and biologic therapies for the treatment of recurrent glioblastoma (GBM).
- The efficacy of this noninvasive treatment modality is achieved with significantly less toxicity and a better quality of life compared with chemotherapy.
- Preliminary data suggest TTF therapy acts synergistically with temozolomide and other chemotherapy in both preclinical and clinical trials.
- Future research should focus on integrating TTF therapy into the treatment of GBM in the adjuvant and maintenance settings, as well as in the treatment of other solid tumor malignancies.

A circular diagram with a central cross-like shape and radiating lines. The central shape consists of a vertical line with four horizontal bars extending from it, resembling a stylized cross or a molecular structure. From the top and bottom of this central shape, several lines radiate outwards, forming a circular pattern around the center. The entire diagram is enclosed within a circle.

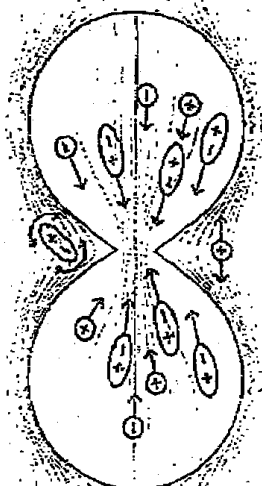


Fig. 2. Effects of further twisting. (A) Side view of a helical structure during twisting. (B) During untwisting, helical structures align with the external electric field, interacting with the formation of the inhomogeneous field. (C) During untwisting, the polarization of the field term within the twisting cell drives charged and polar molecules and argonelles toward the elongation of the helix.

ology, they used antibodies (clinical, laboratory, and pathologic) and demonstrated that TTP therapy in well-preserved rodents does not lead to systemic toxicity in animals, as expected by the frequency ranges of TTP therapy (300–500 kDa), times electric fields do not have any effect on extracellular spaces (central, interstitial, or cardiac), nor do they cause significant heating. 25-25

Clinical Testing of TTF Therapy as a Monotherapy

The NOVOTEST device was first applied to patients in a small feasibility trial in Switzerland in 2001.²⁹ In 2004, a phase I safety study was conducted in a phase III clinical trial in patients with recurrent CRMA (Table 5).³⁰ This single-center, single-arm trial included patients with favorable prognostic character-

Table 1. *In Vitro* Endocrine Overflows[illegible]

Abbreviations: T17, tumor treating regimen; N/A, not available; I was not requested by the authors; "Effect" seen at this frequency; all observed frequencies were not tested

TTF THERAPY IN GLIOBLASTOMA

Table 2. In Vivo Evidence Overview

| Tumor Type | Anatomic Location | Animal Model | Frequency (Hz) | Effect of TTF | References |
|-----------------------------------------|-------------------------------|-----------------|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| GBM | Right hemisphere | Rat | 200 | Tumor growth inhibition with 2 and 3 field directions | <i>Proc Natl Acad Sci U S A</i> , 2007 ⁸ |
| Non-small cell lung cancer | Lung parenchyma | Mouse | 150 | 1. Tumor growth inhibition with 2 field directions 2. Additive tumor inhibition with peritumoral | <i>EBJ</i> , 2010 ⁹ |
| Malignant melanoma | Intradermal | Mouse | 100 | Tumor growth inhibition with 1 and 2 field directions | <i>Clin Lett</i> , 2004 ¹⁰ <i>Proc Natl Acad Sci U S A</i> , 2007 ¹¹ |
| Malignant melanoma VK-2 (melanocyte) | Intravenous Kidney capsule | Mouse Rabbit | 100 150-200 | Inhibition of metastatic seeding in the lungs 1. Tumor growth inhibition seen with 2 field directions 2. Increase in median survival 3. Inhibition of metastatic seeding in the lungs 4. Additive tumor inhibition with peritumoral | <i>Clin Exp Metastasis</i> , 2009 ¹² <i>Clin Exp Metastasis</i> , 2009 ¹³ <i>AACR</i> , 2009 ¹⁴ <i>Neuro Oncol</i> , 2010 ¹⁵ |

Abbreviations: GBM, glioblastoma

letics. Treatment with the device was well tolerated, and no treatment-related serious adverse events were reported. Most patients developed grade 1 to 2 contact dermatitis beneath the transducer arrays on the scalp. Efficacy endpoints were very encouraging with a 50% objective response rate, progression-free survival (PFS) at 6 months of 50%, median time to progression (TTP) of 26 weeks, and median overall survival (OS) of 62.2 weeks (14.4 months). Compared to the historic results of salvage chemotherapy, these results showed clear activity of TTF therapy when used as a monotherapy in recurrent GBM.¹⁷

Based on the results of this pilot trial, a pivotal phase III, multicenter, randomized (1:1) clinical study was initiated in patients with recurrent GBM (Table 3). The randomized study, which recruited 237 patients between 2006 and 2009, compared the efficacy and safety of monotherapy with the NovoTTF device to that of the best available active chemotherapy according to physician's choice. Thirty-six patients received bevacizumab, 80 received nitrosoureas, 12 received temozolomide, and 38 received other agents. This was the largest randomized study in recurrent GBM to be completed to date. The results of the study were presented at the 2010

ASCO Annual Meeting and were updated at the 2011 Society for Neuro-Oncology (SNO) Annual Meeting.^{18,19} Baseline characteristics of patients were balanced between the two treatment groups. In both groups, patients had poor prognostic predictors compared with previous clinical trials of recurrent GBM (50% of patients were at their second or subsequent recurrence; 50% had failed bevacizumab before entering the trial; and the average tumor diameter was above 5 cm). In the conservative intent-to-treat (ITT) analysis, the study showed that patients with recurrent GBM treated with NovoTTF alone had comparable OS to that of patients who received chemotherapy and/or bevacizumab (8.6 months vs. 8.0 months, respectively; $p = 0.26$; hazard ratio [HR] = 0.86; Table 3). Although NovoTTF did not show superiority over active chemotherapy, it was clear that it was at least as effective as these treatments. Secondary endpoints in the trial were supportive: blinded radiology review showed that PFS at 6 months was 21.4% in the NovoTTF group compared with 15.2% in the chemotherapy group ($p = 0.24$). There were more radiological responses even in the NovoTTF group compared with the chemotherapy group (12% vs. 0%, respectively; $p = 0.07$), including

Table 3. Clinical Evidence Overview

| Indication (Analysis Group) | Trial Phase (# of Subjects) Analysis | Overall Survival (Months) | | Hazard Ratio (p) | Progression-Free Survival (PFS) at 6 Months or Median PFS (Weeks) | | P value | References |
|-------------------------------------------------------|--------------------------------------------|------------------------------|---------|---------------------------|----------------------------------------------------------------------------|-------|----------|-----------------------------------------------------------------------------------------------------------------------------|
| | | ITT | Chemo | | TTF | Chemo | | |
| Recurrent GBM (at first relapse) | Phase I-II (n = 10) | 14.5 m | 6.0 m* | Non-randomized | 50% | 15% | NA | <i>Proc Natl Acad Sci U S A</i> , 2007 ⁸ |
| Recurrent GBM (at second and fourth relapse) | ITT Analysis Phase III (n = 237) | 6.6 m | 6.0 m | HR = 0.86 (p = 0.26) | 21.4% | 15.2% | p = 0.24 | <i>J Clin Oncol</i> , 2010 ¹⁸ <i>Neuro Oncol</i> , 2011 ¹⁹ |
| Recurrent GBM (treated patients only) | ITT Analysis Phase III (n = 210) | 7.8 m | 8.0 m | HR = 0.67 (p = 0.012) | 26.2% | 15.2% | p = 0.03 | <i>J Clin Oncol</i> , 2010 ¹⁸ <i>Neuro Oncol</i> , 2011 ¹⁹ |
| Recurrent GBM (KPS ≥ 80, age < 61) | PP Analysis Phase III (n = 110) | 8.8 m | 4.6 m | HR = NA (p < 0.01) | 25.6% | 7.7% | NA | <i>Neuro Oncol</i> , 2010 ¹⁹ |
| Recurrent GBM (after bevacizumab failure) | Subgroup analysis Phase III (n = 43) | 4.4 m | 3.1 m | HR = 0.65 (p = 0.02) | NA | NA | NA | <i>Neuro Oncol</i> , 2010 ²⁰ |
| Recurrent GBM (TTF versus bevacizumab) | Subgroup analysis Phase III (n = 156) | 6.4 m | 5.0 m | HR = 0.65 (p = 0.048) | 21% | 21% | p > 0.05 | <i>Neuro Oncol</i> , 2011 ²¹ |
| Newly diagnosed GBM (together with temozolomide) | ITT Analysis I-II (n = 10) | 39+ m | 14.7 m* | HR = 0.002 (p = 0.002) | 90% | 50% | NA | <i>BMC Med Phys</i> , 2009 ²² |
| Relapsed advanced NSCLC (together with paclitaxel) | ITT Analysis I-II (n = 42) | 13.8 m | 8.2 m* | NA | 26 w | 26 w | NA | <i>ESMO</i> , 2010 ²³ <i>EBJ</i> , 2010 ²⁴ <i>Expert Opin Invest Drugs</i> , 2010 ²⁵ |

Abbreviations: GBM, glioblastoma; ITT, intention to treat; NA, not available (was not reported by the authors); HR, hazard ratio; PP, per protocol; PFS, progression-free survival; TTF, tumor treating fields; NSCLC, non-small cell lung cancer.

* Single-arm trials with historical control

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Three sustained complete responses in the NovoTTF group compared with none in the chemotherapy group. These results were accompanied by significantly ($p < 0.05$) less treatment-related adverse events with NovoTTF compared with chemotherapy. Patients in the NovoTTF group reported a higher quality of life compared with patients treated with chemotherapy. This analysis was based on the European Organisation for Research and Treatment of Cancer QLQ-C30 and mirrored the lack of chemotherapy-related toxicities in the NovoTTF group. Interestingly, patients in the NovoTTF group reported better cognitive and emotional functioning and much less pain than patients in the chemotherapy group, although these domains of the questionnaire are not related to known side effects of chemotherapy.

To date, several exploratory analyses of the study data have been performed. The first analysis compared patients who received the same "amount" of therapy in both groups. This prospectively defined per-protocol analysis excluded patients from both groups who received less than one predefined treatment course. The analysis demonstrated superior survival in the NovoTTF group compared with the chemotherapy group (7.3 months vs. 0.0 months; $p = 0.012$, HR = 0.17).^{10,11} The rationale behind this analysis is that TTF is a physical modality with an half-life, so that the amount the therapy is stopped, its antiproliferative effect stops as well. In contrast, chemotherapies have measurable plasma and tissue half-lives, which results in continued efficacy and toxicity long after a dose has been given. Therefore, to achieve pharmacokinetic balance in the "amount" of treatment in both groups, this analysis used a simplified criterion that one course of chemotherapy (e.g., 1 day of carboplatin or 6 days of temozolomide) is equivalent to four weeks of continuous TTF therapy.

Two more analyses of the study data were presented at the 2010 and 2011 ESMO Annual Meetings.^{10,12} The first study analyzed known clinical prognostic factors of age and Karnofsky performance status (KPS). This analysis demonstrated that in patients age 60 and younger with a KPS greater than 70, treatment with NovoTTF resulted in superior OS compared with chemotherapy (0.8 months vs. 6.0 months; $p < 0.01$). This survival advantage could be attributed to better compliance with TTF therapy in this group of patients. In support of this finding, a statistically significant correlation was seen in the NovoTTF group between treatment compliance (as measured by the device computerized log file) and OS ($p = 0.0476$).

The second analysis is a post hoc, exploratory analysis of the treatment of 120 patients with NovoTTF compared with 35 patients with bevacizumab. Although without a prespecified analysis in the trial, patients in the study treated with NovoTTF lived significantly longer than those treated with bevacizumab (0.8 months vs. 5.0 months, respectively; $p = 0.048$, HR = 0.46).¹² This analysis included all TTF patients who received either bevacizumab or NovoTTF. Patient characteristics were almost identical and, in fact, favored the bevacizumab group prognostically. Clearly, this analysis cannot be taken as final evidence of superiority of NovoTTF over bevacizumab; however, it should be treated as hypothesis-generating data for future clinical studies. Finally, in the 41 patients who entered the study after bevacizumab therapy failure (approximately 30% of patients in both groups), OS was significantly longer with TTF therapy

than with chemotherapy (4.4 months vs. 3.1 months, respectively; $p = 0.02$). The data for the chemotherapy-treated group is in line with previous publications, which showed that following bevacizumab failure, the survival of patients with recurrent GBM is limited.²³

Based on the results of this pivotal phase III study, the FDA approved the NovoTTF-100A device on April 8, 2011, through the premarket approval (PMA) regulatory pathway. The PMA pathway is reserved for class III (high-risk) medical devices and requires preclinical, clinical, and manufacturing evidence, including review of both efficacy and safety data by a panel of independent experts. The FDA concluded that the study results showed NovoTTF to be comparable in efficacy to active chemotherapy, without many of the side effects associated with chemotherapy and with a better quality of life.²⁴

Clinical Trials Evaluating TTF Therapy in Combination with Chemotherapy

Two studies of combined TTF therapy and chemotherapy have been published to date. The first was a single-arm, single-center trial performed in 2008 in patients with newly diagnosed GBM.²⁵ Patients received the Stupp protocol with TTF therapy added to maintenance temozolomide.²⁴ This trial showed promising PFS and OS data (PFS > 14 months; OS > 38 months; Table 3) and served as the basis for an ongoing, multicenter, pivotal phase III, randomized clinical study comparing TTF therapy and temozolomide with temozolomide alone in the maintenance stage of the Stupp protocol.

The second study tested TTF therapy together with pemetrexed in 42 patients with pretreated, advanced non-small cell lung cancer.^{26,27} Efficacy and safety with this combined treatment paradigm were promising. Time to local disease progression in the lungs and liver (where TTF was applied) was 28 weeks, and OS was 13.8 months. In contrast, TTF and OS for pemetrexed alone were previously reported to be 12 weeks and 8.9 months, respectively.²⁸

TTF therapy is still in its early days. However, it has an established mechanism of action, and a growing body of preclinical evidence has shown its wide applicability in solid tumor malignancies either alone or in combination with standard chemotherapies. Objective antitumor activity and an unprecedented safety profile of this treatment modality have been seen in patients with recurrent GBM. Although TTF radiotherapy has been shown to be at least as effective as the best available chemotherapies today for recurrent GBM, in-depth analysis of the phase III study data identified at least two subgroups where TTF therapy was superior to chemotherapy and could be offered to patients as an alternative to chemotherapy: younger patients with a better functional status and patients in whom bevacizumab treatment has failed in the past.

Conclusion

The approval of TTF therapy for recurrent GBM ushers in a fourth modality of cancer treatment. More importantly, TTF treatment has a superior safety profile, and its minor side effects do not appear to overlap with those of cytotoxic chemotherapy, targeted agents, or antiangiogenesis drugs. Therefore, the rational combination of TTF therapy with specific pharmacologic agents may enhance tumor cell death

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Authors' Disclosures of Potential Conflicts of Interest

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| Employment or Residency Positions | Agencies or Advisory Roles | Books Articles Overseas | Monographs | Research Funding Monographs | Expert Testimony | Other Recognition | Notes |
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Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors

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Communicated by Joseph Schlessinger, Yale University School of Medicine, New Haven, CT, April 5, 2007 (received for review January 15, 2007).

We have recently shown that low intensity, intermediate frequency, electric fields inhibit by an anti-microtubule mechanism of action, cancerous cell growth *in vitro*. Using implanted electrodes, these fields were also shown to inhibit the growth of dermal tumors in mice. The present study extends these findings to additional cell lines (human breast carcinoma MDA-MB-231, and human non-small-cell lung carcinoma H1299) and to animal tumor models (intradermal B16F1 melanoma and intracranial F-98 glioma) using external insulated electrodes. These findings led to the initiation of a pilot clinical trial of the effects of TFields in 10 patients with recurrent glioblastoma (GBM). Median time to disease progression in these patients was 28.1 weeks and median overall survival was 62.2 weeks. These time to disease progression and OS values are more than double the reported medians of historical control patients. No device-related serious adverse events were seen after >70 months of cumulative treatment in all of the patients. The only device-related side effect seen was a mild to moderate contact dermatitis beneath the field delivering electrodes. We conclude that TFields are a safe and effective new treatment modality which effectively slows down tumor growth *in vitro*, *in vivo* and, as demonstrated here, in human cancer patients.

(the inhomogeneous fields) at the bridge separating the daughter cells (Fig. 1J) that interfere with spindle tubulin orientation and induce dielectrophoresis.

It is the aim of this work to further study the effects of ac fields on quiescent and proliferating cells in culture, animal cancer models, and cancerous tumors in humans. Following a basic work on cell cultures (9), we demonstrate here that such fields, termed tumor treating fields (TTFields), are effective when applied by insulated external electrodes to animal cancer models and patients with recurrent glioblastoma (GBM). In a pilot clinical trial conducted on this extremely malignant tumor of glial cell origin (10, 11), TTFields treatment was found to be both safe and effective in slowing tumor progression. These promising results raise the possibility that TTFields could become a new treatment modality for cancer.

Cells in Culture

The effects of a 24-h exposure of four of the most common types of cancer (malignant melanoma, glioma (part of the data for malignant melanoma and glioma cells was taken from ref. 9)), breast carcinoma, and non-small-cell lung carcinoma to TTFIELDS are illustrated in Fig. 2. It is seen that the number of unexposed (control) cells roughly doubles every 24 h, whereas the proliferation rate of the exposed cells is slowed down during exposure and gradually recovers after treatment is terminated (Fig. 2A). The frequency dependency of the effects is depicted in Fig. 2B. It is seen that the optimal frequency is 100 kHz for mouse melanoma (B16F1), 150 kHz for human breast carcinoma (MDA-MB-231), and 200 kHz for rat glioma (F-98). In addition, similar experiments were performed in two human glioma cell lines (U-118 and U-87). In both, the optimal TTFIELDS frequency was identical to rat glioma cell lines (i.e., 200 kHz).

The "dose-response curve," i.e., the relationship between the TTF fields effects and field intensity, is given in Fig. 2C. It is seen that effect on cell division and cell death (by apoptosis) is intensity dependent, the sensitivity being highest for mouse

cancer | glioblastoma | tumor treating fields

Because living cells consist of ions, polar or charged molecules, membranes, and organelles, they are responsive to and often generate electric fields and currents. The electric activity of cells plays a key role in many essential biological processes. The electric fields associated with all of the above phenomena are in the range of 0-10 V/cm, except within cell membranes (1) where they may reach 10⁵ V/cm. Whereas electric fields induce ion flow, polar molecules only orient themselves along the lines of a uniform field (2). However, nonuniform electric fields exert forces on polar molecules forcing them to move toward higher field intensity, a well known process known as dielectrophoresis (3, 4). Electric fields and resulting currents, when sufficiently large, stimulate nerves, muscles, cardiac muscle, etc. Only much larger fields generate heat that may damage cells (5).

In an electric field of alternating direction (ac field) all charges and polar molecules are subjected to forces of alternating direction so that ionic flows and dipole rotation oscillate (Fig. 1). In view of the relatively slow kinetics of the bioelectrical responses, as the ac fields' frequency is elevated, their biological effect (except for heating) is reduced such that, >10 kHz, it becomes negligible. Therefore, it is generally believed that ac fields of 100 kHz or above have no meaningful biological effects (5), although a number of nonsignificant effects have been described (6-8).

In continuation to this belief, we have recently demonstrated (9) that 100 Gb, to 1 Mhz ac fields have significant specific effects on dividing cells. The basis of these effects during cytokinesis was shown to be the unidirectional tug induced by

Author contributions: R.D.K., J.D.M., J.S., Y.W., E.D., and Y.P. designed research; E.D.C., V.D., P.T., J.V., A.P., A.L., M.M., J.S., W.S., M.S., B., O.S., E.D., and Y.P. performed research; E.D. contributed new reagents/analytic tools; E.D.K., V.D., P.T., M., D.M., J.S., P., A.L., J.S., Y.W., C.D., and Y.P. analyzed data; and E.D.K., J.S., and Y.P. wrote the paper.

Conflict of interest statement: Y.P. has a minority holding in Novocyt Ltd, and for members of the company board of directors E.D.K., M., A.M., S.S., Z.D., J.S., and Y.W. are employed in full or part by Novocyt Ltd, and M.S. is a clinical trial consultant to Novocyt Ltd.

Freely available online through the PNAS open access option.

Abbreviations: FEM, femoral element metast; GEM, glioblastoma; OS, overall survival; PFS, progression-free survival at 6 months; TTFields, tumor treating fields; YP, time to distant progression.

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This article contains supplementary information online at www.pnas.org/cgi/content/full/0702161105.

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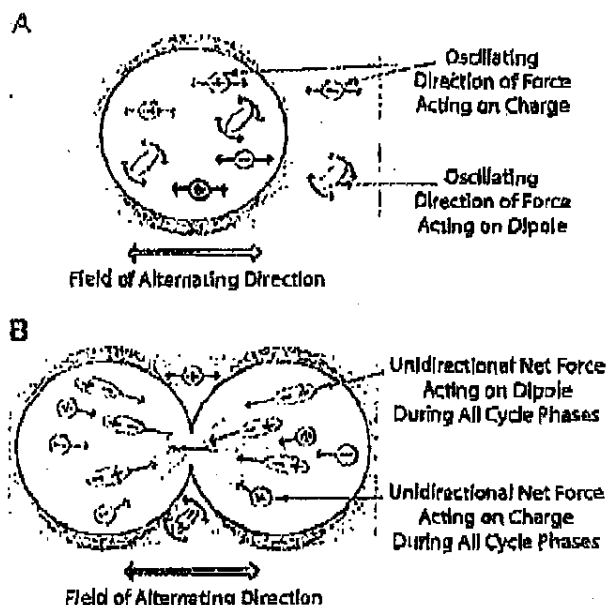


Fig. 1. ac field distribution in and around quiescent (A) and dividing (B) cells. Inside quiescent cells, the field is uniform, and the oscillating electric forces result only in "vibration" of ions and dipoles (the forces associated with each half cycle are denoted white and gray arrows). In contrast, the nonuniform field within dividing cells (B) induces forces pushing all dipoles toward the furrow. Note that at frequencies of 0.1–1.0 MHz, the cell membrane impedance is relatively high, so only a small fraction of the currents penetrate the cells as seen from the density of lines.

melanoma cells, decreasing for rat glioma and for human non-small-cell lung carcinoma and lowest for human breast carcinoma.

From the mechanism of action of TTFields, as illustrated in Fig. 1, it can be deduced that their efficacy must be a function of the angle between the field and axis of division; when the two are parallel its maximal and when one is perpendicular to the

other, it must be minimal. Because in culture the axis of division is randomly oriented, only a fraction of the dividing cells are subjected to optimal treatment. To overcome this problem, multiple field directions were applied sequentially every 0.25–1 sec. Two perpendicular fields were found to be ~20% more effective than the single-direction one for B16F1 and F-98 cells. This result is consistent with the previously reported effects on malignant melanoma cells (9).

Animal Tumor Models

Intracranial Glioblastoma. Our report (9) described the effects of TTFields applied by means of implanted electrodes to intracranial malignant melanoma in mice. This report compares 40 Fischer rats inoculated intracranially with glioma cells, treated by means of external electrodes with a temperature, and geometry matched electrode control group. The treatment duration was 5 days, using the optimal frequency of 200 kHz (see Fig. 2) at 2 V/cm. Fig. 3 depicts the computed field distribution in the rat brain (Fig. 3A), exemplary posttreatment MRI images of a control (Fig. 3B) and a treated tumor (Fig. 3C). The maximal diameter of the treated tumor is about half that of the control one.

The average inhibitory effect of unidirectional TTFields (in a temporal-temporal direction) was small and did not reach statistical significance (treated tumor volume 19.8% smaller than sham control tumors; $n = 26$; $P = 0.19$, Student's t test). However, increasing the number of TTFields directions caused statistically significant inhibition of tumor growth, reaching 42.6% and 53.4% for two ($n = 42$; $P < 0.01$, Student's t test) and three ($n = 10$; $P < 0.01$, Student's t test) directions positioned at 45–90° to each other, respectively.

Frequency Dependence of the Inhibitory Effect of TTFields. The TTFields inhibitory efficacy vs. frequency was studied on mice inoculated with B16F1 melanoma. The mice ($n = 26$) were treated for 5 days by single-direction TTFields of different frequencies. The maximal growth inhibition was found at 100 kHz, with the treated tumor size $62.7 \pm 8.9\%$ that of control tumors. Although this frequency dependence *in vivo* did not reach statistical significance (single-factor ANOVA, $P = 0.11$), it shows the same frequency dependency as the dependence of cultured B16F1 cells reported in ref. 9, which supports the

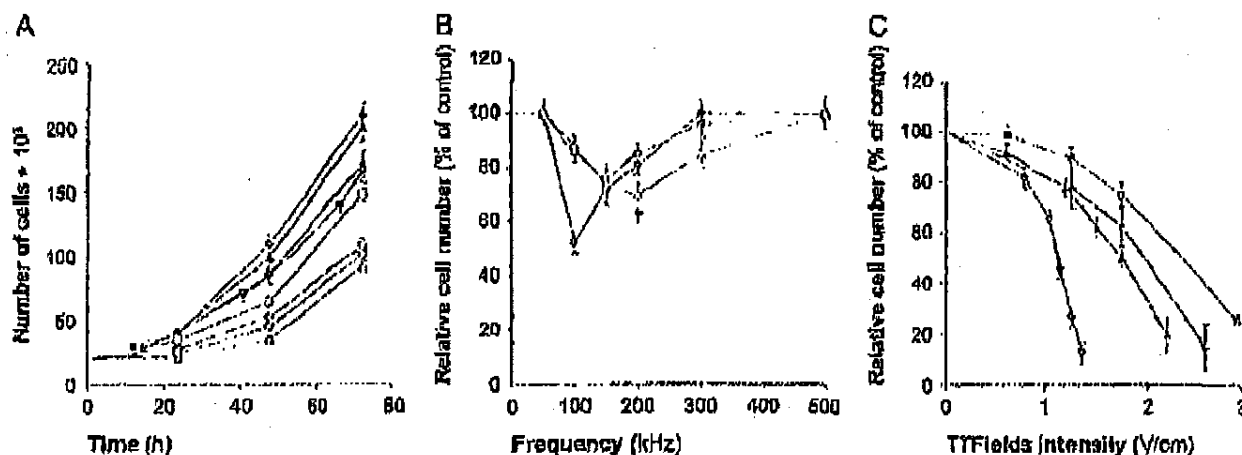


Fig. 2. Time, frequency, and intensity dependence of the effect of TTFields on cancer cell proliferation. (A) The number of cells in untreated cultures (filled symbols) as compared with cultures treated with TTFields (open symbols) for 24 h (1.75 V/cm for MOA-MB-231, F-98, and H1299 cells and 1.1 V/cm for B16F1 cells). (B) The relative change in number of cells after 24 h of treatment of different frequencies (same TTFields intensity). (C) The effect of 24 h of exposure to TTFields of increasing intensities (at optimal frequencies). \circ and \square , B16F1; \triangle and \square , MOA-MB-231; \blacktriangle and \triangle , F-98; $+$ and \circ , H1299.

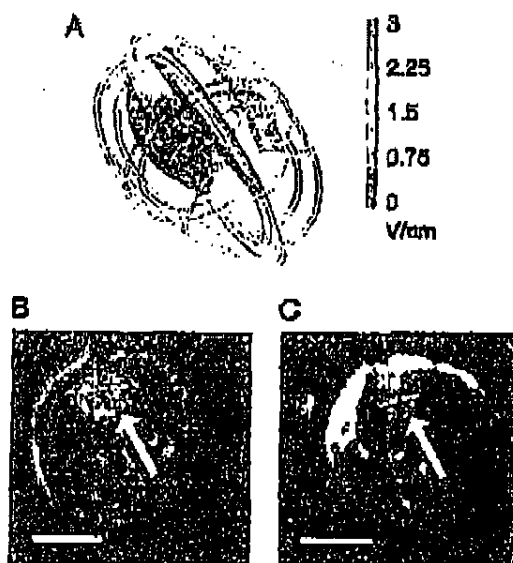


Fig. 3. TTFIELDS inhibition of the growth of intracranial glioma. (A) 3D visualization (using a three-dimensional mesh) of the distribution of TTFIELDS intensity within a simplified rat brain model. (B and C) Exemplary T1 weighted coronal MRI sections (after IV injection of Gd-DTPA) of the heads of a control and a TTFIELDS-treated (200 kHz, two-electrode TTFIELDS) rat, respectively. In both examples, the section shown is that with the largest diameter tumor. Head dimensions are 3.1×1.9 cm (ellipsoid); skin thickness, 0.6 mm ($\sigma = 0.0045$ S/m; $\mu = 1,120$); skull thickness, 1.1 mm ($\sigma = 0.015$ S/m; $\mu = 16$); thickness of the CSF surrounding the brain, 0.5 mm ($\sigma = 2.5$ S/m; $\mu = 100$); and brain itself has the properties of a uniform white matter ($\sigma = 0.15$ S/m; $\mu = 2,200$). The electrodes placed over a 0.5-mm layer of hydrogel. Note the almost uniform field intensity in most brain volume. (Scale bars, 1 cm.)

conclusion that this is the optimum frequency. In contrast, rats bearing intracranial glioma were unaffected by 100 kHz TTFIELDS, whereas 200 kHz TTFIELDS caused significant inhibition of tumor growth.

Safety Profile of TTFIELDS in Healthy Animals. TTFIELDS (100 kHz) at 6 V/cm were applied to the chest of three New Zealand rabbits. No changes were seen in the rate or regularity of cardiac rhythm

throughout and following the exposure. To test the safety of chronic TTFIELDS application TTFIELDS were applied to either the head ($n = 30$, 1 V/cm for 4 weeks) or the chest ($n = 10$, 3 V/cm for 2 weeks) of New Zealand Rabbits. All animals were assessed weekly for weight, temperature, ECG, CBC, wide chemistry panel and coagulation. After a 1-month follow-up period, all animals were killed and hind samples of major organs examined by a pathologist. No treatment-related toxicities were recorded in any of the animals.

GBM Patients

TTFIELDS Treatment of Patients with Recurrent GBM Brain Tumor. Ten patients with recurrent GBM were included in the trial (see *Materials and Methods* and supporting information (SI) Table 1).

As seen in Fig. 4A, the median time to disease progression (TTP) of the patients is 26.1 weeks (range 3–124 weeks) and the progression-free survival at 6 months (PPS6) is 50% (23–77%; 95% confidence interval). Two of the patients were still progression free at study closure.

The median overall survival (OS) of TTFIELDS treated patients is currently 62.2 weeks (range 20.3–124.0 weeks). These TTP and OS values are more than double the reported medians of historical control patients. Three of the patients are still alive at this time. The Kaplan-Meier survival curve (12) of the treatment results is shown in Fig. 4B.

The TTFIELDS treatment resulted in one complete response (Fig. 5A) which is still tumor free per MRI 10 months after stopping treatment and one partial response (Fig. 5B) that is still responding 7 months after stopping treatment. Both are still progression free >2 years from treatment initiation. In addition one patient had minimal response and four had stable disease for over 4 months before progressing.

Safety Profile of TTFIELDS Applied to GBM Patients. The 10 recurrent GBM Patients received treatment for a total of 280 weeks without a single treatment-related serious adverse event and no significant changes were seen in serum chemistry or blood count in any of the patients. The only changes seen consistently were elevated liver enzymes, attributed to anti-epileptic drug usage. Two patients had partial seizures that were unrelated to treatment. Nine of ten patients suffered from a mild to moderate contact dermatitis beneath the electrode gel. This treatment-related adverse event responded well to application of steroid creams and periodic electrode relocation.

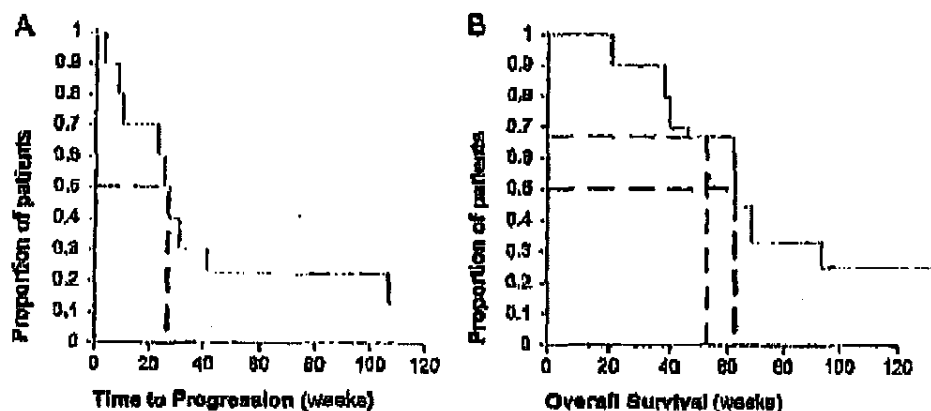


Fig. 4. Efficacy of TTFIELDS treatment in recurrent GBM. (A) TTP of treated patients ($n = 10$); median TTP is 26.1 weeks (dashed black line). (B) Kaplan-Meier OS curve for NovoTTF-100A treated patients ($n = 10$). The median OS in these patients is 62.2 weeks (black dashed line), and the 1-year survival rate is 67.5% (blue dashed line).

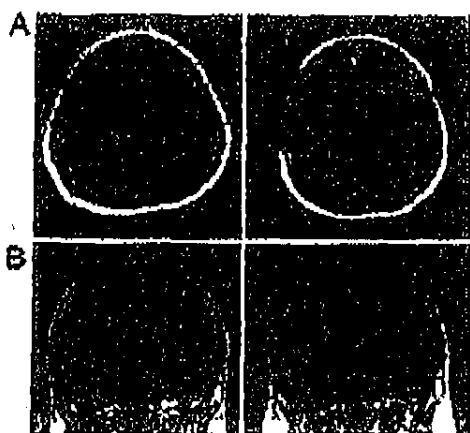


Fig. 5. Exemplary T1-weighted, post contrast, MRI scans of recurrent GBM patients before (Left) and after (Right) TTF fields treatment. (A) Complete response after 6 months of treatment. (B) Stable disease (10% reduction in contrast enhancing area) after 9 months of treatment.

Discussion

Alternating electric fields have been shown to have a wide range of effects on living tissues. At very low frequencies (<1 kHz), electric fields stimulate excitable tissues through membrane depolarization (13) and have been claimed to stimulate bone growth and accelerate fracture healing (14). However, as the frequency of the electric field increases the stimulatory effect diminishes, whereas above MHz a completely different biological effect, tissue heating, becomes dominant (15, 16).

Alternating electric fields of intermediate frequencies (10 kHz to 1 MHz) were considered not to have any meaningful non-thermal biological effects (5). An exception, are the TTF fields described in ref. 9. This presumed lack of effect of such fields is consistent with the fact that when electric fields, that exert forces only on charges and dipoles reverse direction at a high frequency, their net effect tends to null out. Thus, the effects were minor and have neither been shown to be beneficial or detrimental to humans (5, 6, 17).

In this study we try to use TTF fields as a new cancer treatment modality. We first extended the *In-Vitro* study of TTF fields effect on glioma and melanoma cells (9) to several of the most prevalent cancers; breast carcinoma and non-small-cell lung carcinoma. It was found that the proliferation of these cells is arrested and the cells are destroyed (Fig. 2). The optimal frequencies differed between cancer cell types. To understand this finding we calculated the force on a 1 μ m polarizable spherical particle in a dividing cell as function of cell radius, membrane thickness and cytoplasm conductivity. It was found that optimal TTF fields frequency is inversely related to cell size (see *SI Appendix A*) in a way consistent the diameter variability of the different cell types studied.

In the previous study (9) animal treatment was done by using implanted electrodes. In the present study, we used the much more practical externally applied electrodes. Furthermore, as the available data suggests that treatment may need to be prolonged, the use of conducting electrodes may result in serious problems: local damage to the skin because of electrolysis and the generation of free radicals at the electrode-tissue interface, skin permeabilization by the transdermal currents (18, 19), and calcium accumulation within cells (20) that can result in cell death (21). Clearly, the first 2 adverse effects do not occur at the surface of insulated electrodes. Using fluorescence calcium imaging techniques, we could demonstrate that electric field

induced calcium accumulation is eliminated by the use of insulated electrodes (see *SI Appendix B*). However, the large potential drop across the insulation high impedance poses a serious problem; to generate the fields of the required intensity potentials of $>1,000$ V must be used. At such high voltages may compromise patient safety, low impedance electrodes were developed. The impedance of insulation is lowered by using an insulating material, lead tungsten dioxide-lead titanate (PMN-PT) (BDO, New York, NY), that has a dielectric constant of $\epsilon > 3,000$. Under these conditions the electrodes have a capacitance of ~ 10 nF/cm², i.e., an impedance of 100–200 Ω at the TTF fields frequency range. Thus, only 50% of the applied voltage is lost on the insulation in the mice experiments. The corresponding potential drop on the 22.5 cm² electrodes placed on the patient's head, in the trial presented here, is only $\sim 10\%$ of the applied voltage.

A major limitation of all current cancer treatments is their unfavorable therapeutic index. Two types of toxicities may be expected from an electric field based treatment. First, the fields could theoretically affect excitable tissues causing cardiac arrhythmias or seizures. However, such effects are not expected to occur, because for sinusoidal alternating fields of >10 kHz, excitation of nerves and muscles decreases dramatically, because of the parallel resistor-capacitor nature of the cell membrane (22). Indeed, in both acute and chronic application of TTF fields to animals and patients, there was no trace of abnormal cardiac or neurological activity. Secondly, TTF fields might be expected to damage rapidly dividing normal cells within the body, i.e., bone marrow and small intestine mucosa. However, no treatment-related toxicities were found in any of the treated patients or upon animal exposure to field intensities threefold higher than the effective anti-tumoral dose. With regards to hematopoiesis the reason for this is that these cells, which reside mainly in the bone marrow, are protected from the TTF fields by the high impedance of both the bone and bone marrow (23). This was demonstrated by calculating the TTF fields distribution in an extremity, such as a leg, by using the finite element mesh (FEM) method. It was found that the field intensity is 100 fold lower within the bone marrow compared with the surrounding tissues. The lack of damage to intestinal mucosa probably reflects that the small intestine mucosal cells have a slower replication cycle than neoplastic cells (24) and that the intestine changes its orientation, relative to the applied field, often lowering the efficiency of the mitotic disruption.

The tumor inhibitory effect of TTF fields has been attributed previously to two separate mechanisms (9): interference with the formation of the mitotic spindle microtubules and physical destruction of cells during cleavage, both of which are strongly dependant on the orientation of mitosis axis versus the field vectors. Because the relative orientation of the mitosis axis during cytokinesis is random, it would be expected that only a fraction of dividing cells would be affected by TTF fields of any specific direction. To overcome this problem, we applied sequentially several field directions and have shown that increasing the number of directions from 1 to 3, resulted in a significant increase in the anti-proliferative efficacy of TTF fields *in vitro* and *in vivo*.

Following encouraging evidence from experimental animals, a clinical trial of the effect of TTF fields on patients with recurrent GBM was initiated. Because *in vitro* data indicate that TTF fields are most effective when applied for >16 h continuously (data not shown), patients were treated daily for an average of 18 h per day until progression. The results reported here are the first evidence of the safety and efficacy of TTF fields used to treat cancer in patients. Preliminary accounts of this data were published in

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abstract from NASS. Because this was a pilot trial there was no randomized control group and the results were evaluated by comparing to historical control data. Most historically controlled pilot studies in recurrent GBM are compared with a large metaanalysis performed by Wong *et al.* in 1999 (10) and to this data we added the four prospective trials (25-28), which included >50 GBM patients, performed since that date. The average historical PRS6 based on the above studies is $15.3 \pm 3.8\%$, and the average historical TTP is 9.5 ± 1.6 weeks. OS averaged 29.3 ± 6 weeks (see SI Table 2). When compared with these outcomes, the efficacy data collected in the current pilot trial is extremely promising (TTP, 26.1 weeks; PRS6, 58%; and OS, 62.2 weeks). These results were not accompanied by hematological or gastrointestinal toxicities, epileptic seizures, cardiac arrhythmias, etc., despite >70 months of cumulative treatment. The only side effect detected was contact dermatitis beneath the electrodes. This reaction is most likely the result of a combination of factors, including chronic moisture, heat, and occlusion of the skin; chemical irritation by constituents of the hydrogel and medical tape (29); and possibly inhibition of cellular repigmentation in the skin by the TTFs. Thus, in conclusion, this treatment modality was well tolerated and caused almost no toxicity at all.

In summary, we demonstrated initially that TTFs are effective in arresting the proliferation and inducing death in a wide range of tumor cells in culture as well as solid tumors in animals. On this basis a clinical trial was carried out treating human patients suffering from recurrent GBM, a malignant brain tumor. It was demonstrated that the TTFs inhibit the growth of this highly treatment-resistant tumor by using special insulated electrodes, with little or no side effects. Can we expect to have similar efficacy on other human tumors? The fact that in cultures and animal models TTFs were found to be effective on all cells and tumors tested is definitely encouraging. Furthermore, TTFs being a physical, rather than chemical, modality, their efficacy is likely to be highly insensitive to specific interactions with tumor and patient receptors and other characteristic elements. Thus, like irradiation, they have the potential to be effective over a wide range of tumors. However, from the above it is apparent that their practical specificity to cancerous cells is significantly higher than that of irradiation, the therapeutic efficacy of which is often severely limited by toxicity. Therefore, we believe that there is a high probability that TTFs may prove to be an effective and safe therapeutic modality to a large number of human cancers.

Materials and Methods

Cell Cultures. Cell cultures were grown in DMEM plus 10% FCS media in a CO₂ incubator (5% CO₂) at 37°C. Cell suspension (200 µl; total 20×10^6 cells) were placed as a drop in the center of 35-mm Petri dishes, incubated for 24 h and then the cell number was estimated by using standard XT method (Cell proliferation assay Kit, Biological Industries Ltd., Israel) and expressed as OD₅₅₀. Temperature was monitored by a thermocouple (Omega, Stamford, CT) placed at the center of the dish. Two pairs of electrodes, insulated by a high dielectric constant ceramic (lead magnesium niobate-lead titanate (PMN-PT)), positioned in the petri dish perpendicular to each other were connected to a sinusoidal function generator and amplifier. Two-directional fields were generated sequentially (1) by switching the output of the amplifier between two pairs of electrodes every

0.25–1 sec. The electric field intensity in the culture medium was measured as described in ref. 1.

At the end of 24 h of treatment, the cell number was measured by using the XT method and expressed as OD₅₅₀. The rate of cell proliferation was expressed as the OD₅₅₀/OD₀ ratio.

Animal Models. Tumor inoculation and in vivo size assessment. Animal experiments were conducted after approval by the Technion-Israel Institute of Technology committee for the care of laboratory animals. Intracranial glioma (P-98) was inoculated stereotactically into the subcortical white matter in the right hemisphere of Fischer rats (Taconic Laboratories, Israel) by using a modification of the method described in refs. 30 and 31. Briefly, a hole, 1 mm in diameter, was punched through the scalp, 2 mm to the right of the midline and 4 mm rostral to the line connecting the external ear canals. A 0.5 mm burr hole was drilled in the bone at same location and a 26G needle was inserted to a depth of 7 mm beneath the scalp surface. Five microliters of saline containing 2.5×10^5 P-98 cells was then injected by using a microsyringe operated by a micromanipulator. The needle was left in position for 60 sec and then retracted slowly at a rate of 2 mm/min. Rats were allowed to recuperate for 24 h before treatment initiation. Tumor volume was assessed based on serial (2-min interval) T1 weighted axial MRI images (0.5 Tesla MRI; Gyrex orbital coil; Elscint, Haifa, Israel) obtained 10 min following injection of 0.7 ml of Gadolinium (Magnevist; Soreq Radiopharmaceuticals, Yavne, Israel) into the tail vein. Tumor volume was assessed by calculating the area in square millimeters of the contrast enhanced lesion in each section. In view of the small size of the head of the rat, only three electrodes could be positioned on it, generating one to three different field directions.

Computation of the distribution of electric fields generated by external insulated electrodes. The distributions of the alternating electric field generated by external electrodes within the brains of rats were estimated by using FEM simulations. These field distributions are determined by the geometry and electrical properties of the electrodes and tissues. On average, the capacitance of each electrode is 8 nF. This translates into an impedance of 190 and 93 Ω at 100 and 200 kHz, respectively. Because the impedance of the rat head is on the order of 400 Ω, when applying 42 V, 200 kHz TTFs to rats, 14-V drop on the insulation of both electrodes and the remaining 28 V on the rat itself. The fields generated in the areas of interest are in the range of 1–2 V/cm. The calculated field distribution for the rat head is given in Fig. 3A.

Human GBM Trial. GBM patient eligibility and characteristics. Twelve patients, suffering from the brain tumor GBM were enrolled to the study. Patients eligible for enrollment had recurrence based on Macdonald criteria (32), were >18 years old, had histologically established GBM (World Health Organization grade IV), had a Karnofsky performance scale ≥ 70 , and were at least 4 weeks from any brain surgery and at least 8 weeks from radiotherapy. Patients could be at any recurrence and may have received other salvage therapies before enrollment. All patients had received adjuvant Temozolomide for their primary tumor. No concomitant chemotherapy was allowed. Multifocal disease was allowed. Patients with significant comorbidities, intracranial tumors, implanted pacemakers or documented clinically significant arrhythmias, were excluded from the trial. During review of the histology from postresection debulking surgery, one patient was excluded from efficacy analysis because of failure to meet histological criteria for grade IV glioma. An additional patient dropped out of the trial immediately following the baseline visit because of withdrawal of consent. Individual patient characteristics are listed in SI Table 1.

¹⁰Kuzon, E. D., Oshali, V., Ilchik, C., Tover, P., Spitzberg, M., Palt, V., AACR Meeting Abstracts, April 2, 2005, Washington, DC, Abstract 5253.

¹¹Oshali, V., Kiran, E. D., Palt, V., Gulin, P.H., Congress of Neurological Surgeons, October 13, 2005, Boston, MA (abstr.).

¹²Gulin, P., Kiran, E., Palt, V., Oshali, V., International Brain Tumor Research and Therapy Meeting, April 20, 2005, Napa Valley, CA (abstr.).

The clinical trial A single arm, pilot trial of the safety and efficacy of TTFields treatment was performed in 10 patients with recurrent GBM. Written informed consent was obtained from each subject. The trial was performed after approval by the Na Homolce Institutional Review Board and the Czech Ministry of Health. Efficacy analysis was performed for 10 recurrent GBM patients by comparing TTP, PFS6, and OS in recurrent GBM patients treated with the NovoTTP-100A device with the TTP, PFS6, and OS of recurrent GBM patients in a literature based historical control group (10, 25–28). No statistical hypothesis testing was planned because of the small sample size. Ninety-five percent confidence intervals of survival proportions were calculated from Kaplan-Meier survival curves, by using standard formulae (33).

Measurement and simulation of TTFields intensity within the human brain. To plan the TTFields intensity necessary to treat patients with intracranial tumors, we performed FEM simulations of the intensity distribution of TTFields within a three-dimensional model of the human head. Field intensity was slightly higher in the cortex than in the center of the brain (by ~30%), but effective (1–2 V/cm) TTFields could be generated at the center of the brain by applying ~50 V to surface electrodes placed on the scalp. To validate these findings, TTFields intensity was measured within the brain of a volunteer undergoing surgery because of obstructive hydrocephalus because of a huge meningioma of the pineal region. The study was performed according to an experimental protocol approved by the Rambam Medical Center ethics committee. The measured TTFields intensity was accurate within 10% of the FEM simulated values.

TTFields treatment of GBM patients. TTFields were applied to recurrent GBM patients by using the NovoTTP-100A device (NovoCure Ltd., Haifa, Israel). This portable battery-operated device generates TTFields in GBM patients by means of insulated electrodes placed on their shaved scalps. The area of each

insulated electrode array used was 22.5 cm². Fields of 1–2 V/cm were generated by controlling the current density through the electrodes <31 mA/cm² RMS, approximately one-third of the level that is generally recognized to present a risk of skin injury (100 mA/cm²) (34). In addition, the maximal power density beneath the electrodes was kept beneath 0.32 W/cm², i.e., below the level associated with thermal skin injury (35). Electrode temperature was monitored and the power was lowered automatically when the temperature of any electrode exceeded 41°C. This value is well below the threshold of 44°C, i.e., the lowest prolonged temperature that can cause thermal injury (34).

TTFields having the optimal frequency of 200 kHz for rat and human gliomas (see Fig. 2) and an intensity of 1–2 V/cm (peak) were used in the trial. TTFields were switched sequentially every 1 sec between two perpendicular directions; lateral and anterior-posterior, through two sets of insulated electrode pairs. Patients received treatment continuously until disease progression or for a maximum of 18 months. Treatment was applied daily for an average of 16 h per day.

Patient evaluation. Objective tumor assessment was performed by Gd-enhanced MRI according to a strictly defined protocol. MRI scanning was performed at trial entry within one week of NovoTTP-100A treatment initiation and after every treatment course (28–30 days). All scans were reviewed by a board certified radiologist (J.V.). The assessment of tumor response was based on criteria defined by Macdonald et al. (32). Study visits were performed once per week during the first month of treatment and monthly thereafter. The following examinations were carried out at each visit: Neurological evaluation, EKG, complete blood count with differential, chemistry panel, and coagulation studies. Adverse events occurring during treatment or up to 60 days after termination of therapy were scored according to the common toxicity criteria scale (version 3). Disease progression was not captured as a serious adverse event.

This work was supported by NovoCure Ltd.

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(CANCER RESEARCH) 32(1) 194, May 1, 2001

Disruption of Cancer Cell Replication by Alternating Electric Fields

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ABSTRACT

Low-intensity, intermediate-frequency (100–300 kHz), alternating electric fields, delivered by means of insulated electrodes, were found to have a profound inhibitory effect on the growth rate of a variety of human and rodent tumor cell lines (Panc1a C, U-118, U-87, H-1299, MDA231, PC3, B16F1, F-98, C-6, RG2, and CT-26) and malignant tumors in animals. This effect, shown to be nonthermal, selectively affects dividing cells while quiescent cells scratch intact. These fields act in two modes: arrest of cell proliferation and destruction of cells while undergoing division. Both effects are demonstrated when such fields are applied for 24 h to cells undergoing mitosis that is oriented roughly along the field direction. The first mode of action is manifested by interference with the proper formation of the mitotic spindles, whereas the second results in rapid disintegration of the dividing cells. Both effects, which are frequency dependent, are consistent with the computed directional forces exerted by these specific fields on charges and dipoles within the dividing cells. In vivo treatment of tumors in C57BL/6 and BALB/c mice (B16F1 and CT-26 syngeneic tumor models, respectively), resulted in significant slowing of tumor growth and extensive destruction of tumor cells within 3–6 days. These findings demonstrate the potential applicability of the described electric fields as a novel therapeutic modality for malignant tumors.

INTRODUCTION

In the laboratory setting and in clinical practice, alternating electric fields show a wide range of effects on living tissues. At very low frequencies (under 1 kHz), alternating electric fields stimulate excitable tissues through membrane depolarization (1). The transmission of such fields by radiation is insignificant, and therefore they are usually applied directly by contact electrodes, although some applications have also used insulated electrodes. Some well-known examples of such effects include nerve, muscle, and heart stimulation by alternating electric fields (1, 2). In addition, low-frequency pulsed electric fields have been claimed to stimulate bone growth and accelerate fracture healing (3). However, as the frequency of the electric field increases above 1 kHz, the stimulatory effect diminishes. Under these conditions, although a greater fraction of the fields penetrates the cells, due to the parallel resistor-capacitor nature of all biological membranes, the stimulatory power greatly diminishes as the alternating cell membrane hyper-depolarization cycles are integrated such that the net effect is nullified. At very high frequencies (i.e., above many MHz), although the integration becomes even more effective, a completely different biological effect is observed. At these frequencies tissue heating becomes dominant due to dielectric losses. This effect becomes more intense as frequency, field intensity, or tissue dissipation factor increases (4). This phenomenon serves as the basis for some commonly used medical treatment modalities including diathermy and radio frequency tumor ablation, which can be applied through insulated electrodes (5). Intermediate-frequency electric

fields (i.e., tens of kilohertz to megahertz) alternate too fast for causing nerve-muscle stimulation and involve only minute dielectric losses (heating). Such fields of low to moderate intensities are commonly considered to have no biological effect (4). However, a number of nonthermal effects of minor biological consequence have been reported even at low field intensities. These include microscope periodic alignment (i.e., the pearl chain effect; Ref. 6) and cell rotation (7, 8). With pulsed electric fields of 10^3 V/cm and 100-ns pulse length, reversible pore formation appears in the cell membrane, a phenomenon usually called electroporation (9).

In the present study we show for the first time, to our knowledge, that very low-intensity (<2 V/cm), intermediate-frequency (100–300 kHz), alternating electric fields induced by insulated electrodes have specific inhibitory effects on dividing cells in culture. We demonstrate that applying these fields to cancerous cells leads to proliferation arrest and cell destruction. When applied to syngeneic mice tumor models, these tumor treating fields (TTFields) cause a significant reduction in tumor growth rate without any significant side effects.

MATERIALS AND METHODS

In Vitro Experimental Set Up. Cultures were grown in standard culture dishes (4-well) cell culture chambers; SN 13821; Nalga Nunc International). The TTFields were generated by pairs of 15-mm-long, completely insulated wires (WV K-30-1000; VT Corporation; outer diameter, 0.5 mm; ethylene tetrafluoromethylene insulation thickness, 0.125 mm; dielectric breakdown, 1800 V/mil) fixed to the bottom of each dish at a distance of 1 mm from each other. The wires were connected to an oscillator (GSG8219A; Instek) and a high-voltage amplifier (A303; A. A. Lab Systems Ltd.) that generated the required sine-wave signals (range, 300–800 V). Cells were plated by carefully seeding 10^4 cells along the gap between the wires (Fig. 1A). After the cells settled and attached to the plate surface, 500 μ l of DMEM were added to each culture dish, which was then transferred to a 5% CO₂ humidified incubator held at 36°C. The culture was incubated for a control period of 24 h before treatment. Culture medium was replaced manually every 24 h throughout the experiments. TTFields were then applied by connecting the wires to a high-voltage amplifier operated by a signal generator with frequency and amplitude controls. Finite element simulation of the TTFields generated between the wires demonstrated that the field in the vicinity of the cell culture was homogeneous (not shown). Eleven different types of cancerous cell lines were subjected to TTFields. These included human melanoma (Panc1a), glioma (U-118, U-87), Lung (H-1299), prostate (PC3), and breast (MDA231) cancerous cell lines as well as mouse melanoma (B16F1), rat glioma (F-98, C-6, and RG2), and mouse adenocarcinoma (CT-26) cell lines (all from American Type Culture Collection, except for Panc1a, which was a generous gift from Dr. Ruth Itzhaki, Department of Dermatology, Yale University School of Medicine). In addition, a noncancerous cell line (BHK) was grown under conditions that stunt cell replication (0.1% PC9) and then subjected to TTFields. Also, segments of excised rat mammary and diaphragm were subjected to the fields *in vitro*. Coliformic cell counts were made every 24 h after seeding using the standard 2,3-bis(4-methoxy-4-nitro-5-sulfinophenyl)-5-[(phenylamino)carbonyl]-2H-tetrazolium hydroxide method to measure cell proliferation as described previously (10) using cell proliferation assay kit (Biological Industries, Beit Haemek, Israel). In brief, culture media was replaced with 0.2 ml of prelabeled 2,3-bis(4-methoxy-4-nitro-5-sulfinophenyl)-5-[(phenylamino)carbonyl]-2H-tetrazolium hydroxide reagent and incubated for 1 h at 37°C in a 5% CO₂ incubator. After incubation and gentle stirring,

Received 1/1/04; revised 2/1/04; accepted 2/17/04.
Grant sponsor: NovoCure Ltd.

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0.15 ml of the reaction solution was transferred to a 96-well plate (SN 92696; TPP, Transduction, Switzerland). The absorbance of the complex was then read with a spectrophotometer (Faxco BLISA Reader; 450 nm). The conductance measurements at each time point were normalized to the measurement performed immediately before beginning of treatment. To verify that the conductance measurements were accurate, direct visual cell counts were performed on sample culture dishes. At the optic densities used (0.2–2), optic density was linearly related to the number of cells in the culture dishes ($n = 10$; $r^2 = 0.99$). The growth rate of both treated (QR_t) and control cultures (QR_c) was calculated for each experiment by plotting the optic density values on a logarithmic scale and fitting a linear regression line to the values. The growth rate for each culture dish was the slope of this linear regression. The therapeutic enhancement ratio (TER) was calculated as the ratio of the decrease in the growth rate of treated cells compared with the growth rate of control cells ($(QR_c - QR_t)/QR_c$). Thus, if the increase in the number of treated cells is equal to that of the controls, $TER = 0$; if the increase in cell number is smaller in the treated cultures than in the controls, $TER > 0$; and if the number of cells in the treated cultures decreases absolutely, $TER > 1$.

In three-phase microparticle-trap experiments, cell lines were grown on a 35-mm standard culture dish (SN 430165; Corning Inc.) by plating 3×10^5 cells in 2.5 ml of DMEM with 25 mM HBES. The four dish temperature was controlled at 34°C (B16F1) or at 37°C (all other cell lines). Subsequently, two parallel insulated wires were positioned on the bottom of the dish with 1 mm distance between them through which TTFs were applied. The entire set-up was placed on an inverted microscope (Eclipse TS-100; Nikon) and video microphotographs at $\times 200$ magnification were taken with a standard VCR camera (Handicam X 320; Sony). Photographs were captured using a personal computer every 60–120 s for 6–10 h/culture.

Fluorescent Labeling of α -Tubulin, Actin, and DNA. Mouse melanoma cells were grown on coverslips and subjected to TTFs for 24 h. After treatment, the medium was removed, and the cells were washed in a buffer solution [10 mM 4-morpholinethanesulfonic acid, 150 mM NaCl, 5 mM EGTA, 5 mM MgCl₂, and 5 mM glucose (pH 6.1)], permeabilized, and fixed with 0.5% Triton X-100 and 0.25% glutaraldehyde (Sigma) for 5 min and then post-fixed with 1% glutaraldehyde for 20 min. Subsequently, the cells were washed in PBS and 1 mM sodium borohydride (Sigma) to eliminate autofluorescence. The coverslips were then incubated with a primary antibody clone for α -tubulin (DM1A; Sigma) for 30 min, washed, and incubated for 30 min with a secondary antibody (Alexa Fluor 488 goat anti-mouse IgG; Molecular Probes). Rhodamine-conjugated phalloidin (Sigma) was added with the secondary antibody to stain actin filaments. The cells were then washed and incubated with 4',6-diamidino-2-phenylindole (Molecular Probes) to stain the DNA. After staining, the coverslips were mounted and viewed with a fluorescence microscope at $\times 630$ magnification and photographed.

Electric Field Measurement. The electric field intensity in the culture medium was measured by means of a probe, consisting of two (0.25 mm in diameter) insulated wires with exposed tips 0.5 mm apart, that was dipped in the culture medium. The wires were connected to a high-input impedance differential amplifier that translated the waveform amplitude into a calibrated steady voltage that was digitally recorded. Field intensities throughout the manuscript are expressed in peak voltage amplitude per centimeter (V/cm). Care was taken to eliminate any pickup from the field outside the culture medium. Continuous field monitoring could also be made by measuring the potential drop across a 100 Ω resistor placed in series with one of the field-generating wires. The voltage drop on this resistor was linearly correlated to the field intensity ($r^2 = 0.96$). To verify that the experimental setup was not exposed to any significant magnetic fields, the electromagnetic radiation in the immediate vicinity of the treated cultures was measured using a loop antenna (EMCO 6507; 1 kHz to 30 MHz) connected to a spectrum analyzer (Anritsu 9 kHz to 2.2 GHz). The electromagnetic radiation in the 100–300-kHz range within the incubators containing treated culture dishes was found to be 10^{-12} Tesla and within animal cages containing TTF-treated mice, 10^{-14} Tesla, i.e., negligible.

Finite Element Simulations of Electric Field Distribution. The calculations of the electric field within the cells are based on finite element mesh (11), using a simplified description of the cell morphology (see Fig. 7). In all calculations, the dielectric constant of both the cytoplasm and medium was 80, their conductance was 0.3 S/m, the cell diameter was 10 μ m, and the membrane thickness was 3 nm (with a dielectric constant of 3). The electric field

intensity was mapped within the cell, based on the amplitude (1 V/cm), frequency (100 kHz) and waveform (saw) of the electric field applied to the cell culture. The force exerted by an inhomogeneous field, such as that created inside the cells on a single tubulin dimer, was calculated based on the direct interaction between the electric field and the dipole. The force exerted on a microscopically polarizable organelle was calculated by the following equation (12):

$$\langle \vec{F} \rangle = 2\pi r^2 \epsilon_m \text{Re}[K(\omega)] \nabla E_{\text{RMS}}^2 \quad (1)$$

where $\langle \vec{F} \rangle$ is the expectation value of the force vector, Re symbolized the real component of the variable, ∇ is the divergence of the variable, ϵ_m is the cytoplasmic dielectric constant, r is the tubulin dimer length or particle radius, E_{RMS} is the RMS value of the electric field, and $K(\omega)$ is the Clausius-Mossotti factor:

$$K(\omega) = \frac{\epsilon_p^* - \epsilon_m^*}{\epsilon_p^* + 2\epsilon_m^*} \quad (2)$$

$$\epsilon^* = \epsilon - j \frac{\sigma}{\omega}$$

where ϵ_p^* , ϵ_m^* are the complex dielectric constants of the particle and cytoplasm respectively, each of which is calculated from the dielectric constant (ϵ) and conductance (σ) as a function of frequency (ω). $K(\omega)$ in this case is always positive at the relatively low frequencies used (i.e., 100 kHz), assuming that at these frequencies, $\epsilon_p > \epsilon_m$. This means that the forces acting on a polarizable particle will always act in the direction of the convergence of the electric field lines. The terminal velocity of particles due to these forces was calculated using Stokes' law.

In Vivo Experimental Setup. TTF treatment was applied by means of 10-min-long pulses of parallel, insulated wires (outer diameter, 0.5 mm; insulation thickness, 0.125 mm; Tefzel) placed intradermally on the back of a mouse. Another pair of identical wires was placed parallel to the first pair in each mouse, with an interval of 5 mm between the pairs. Cell line inoculums were injected (4 μ l; 3×10^5 cells) intradermally in between the two members of each pair of implanted wires. Only one pair was then connected to a voltage amplifier to apply 100 kHz of TTFs treatment to one tumor. The other pair of wires was left disconnected, and the tumor between them served as a paired control of the treated tumor (see Fig. 1B). Tumors were measured using a caliper. Tumor size was calculated by multiplying maximal tumor length by maximal tumor width. Animal experiments were conducted in accordance with the Technion-Israel Institute of Technology guidelines for the care of laboratory animals.

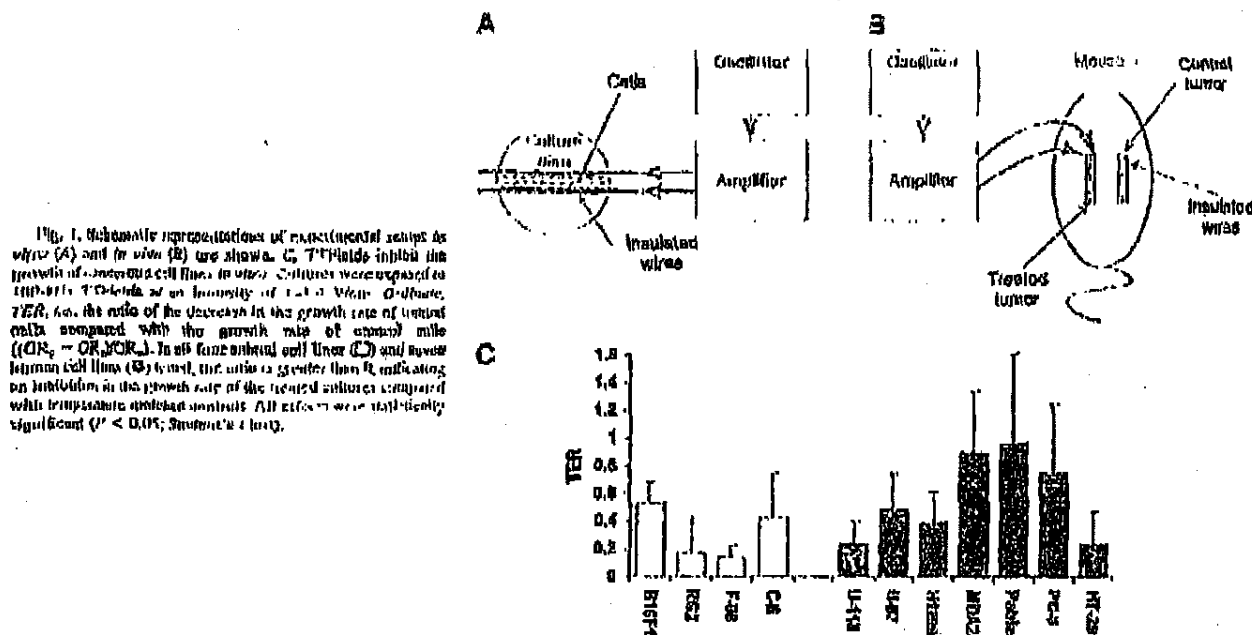
RESULTS

Effect of TTFs on Cells in Culture. More than 500 culture dishes were exposed to TTFs. The number of cells in each treatment dish was assessed periodically using colorimetric determination (as described in "Materials and Methods"). Because under control conditions, most of the cell lines had doubling times of less than 24 h (range, 17–24 h; except for PC-3 for which the doubling time was 73 h), treatment duration was at least 24 h. Exposure began 24 h after seeding and was continued for up to 72 h. In all cell lines tested, 24-h exposure to TTFs at 100 kHz (at an intensity of 1.0–1.4 V/cm) caused significant inhibition of cell proliferation (TER range, 0.14–0.96; $P < 0.05$; Fig. 1C). This effect lasted beyond the exposure time of the cells to TTFs. In fact in some experiments (e.g., malignant melanoma), culture growth was started for as long as 72 h after TTF exposure was terminated (Fig. 2A).

We next checked whether nonreplicating cultures and tissues are affected by TTFs. BHK cultures were maintained in low-serum (0.1% FCS) conditions to slow their replication rate. These cultures were then exposed to 100 kHz of TTFs (at an intensity of 1.2 V/cm) for 24 h. No significant difference in cell number between control and TTF-treated cultures was observed under these con-

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ditions ($P = 0.97$). After returning these cultures to normal media (10% FCS), normal replication resumed both in cultures exposed to TTFs and in control cultures. We also tested the effect of TTF treatment on the number of viable cells in nonreplicating tissues dissected from rats. Four segments of rat mesentery and four segments of rat diaphragm were exposed to 100 kHz of TTFs at an intensity of 1.2 V/cm for 24 h. No differences were observed between the number of viable cells in both types of treated tissues compared with control tissues (mesentery, $P = 0.3$; diaphragm, $P = 0.54$).

To test the relationship between TTF intensity and inhibition of cell proliferation, mouse melanoma (B16F1) and rat glioma (F-98) cell lines were exposed to TTFs of different intensities between 1 and 2.5 V/cm. The inhibitory effect of TTFs on cell proliferation increased as intensity was raised (Fig. 2B) until complete proliferation arrest was achieved at intensities of 1.4 and 2.25 V/cm in melanoma and glioma cells, respectively.

The effects of TTFs are expected to be frequency dependent in view of the dependence of cell membrane electric impedance on frequency (due to the cell membrane capacitance). These changes in impedance render the fraction of field penetrating the cells a function of frequency. Therefore, we tested the frequency dependence of the inhibitory effect of TTFs on growth rate of cultured melanoma (B16F1) and glioma (F-98) cells. Comparison between the efficacy of the TTFs at different frequencies was performed by normalizing the TER to the electric field intensity. As seen in Fig. 2C, the inhibitory effect of TTFs was frequency dependent. Interestingly, the frequency at which maximal inhibition was achieved differed between cell types (120 kHz versus ~200 kHz for melanoma and glioma, respectively).

The Effects of TTFs on Cellular and Molecular Processes in Proliferating Cells. To gain insight into the cellular processes by means of which TTFs affect cell proliferation, time-lapse microphotography was performed while TTFs were applied to mouse melanoma cultures (see "Materials and Methods"). Several unique processes became evident in time-lapse microphotography of TTF-treated cultures. The most pronounced phenomenon was

prolongation of mitosis. In the treated cells, mitosis seemed to begin normally but was prolonged for variable periods of time before completing cleavage into two daughter cells. Fig. 3A shows an exemplary mitosis in a TTF-treated cell. As seen in the treated cell, mitosis was not complete within 3 h. Due to this proliferation arrest, in treated cultures, mitosis lasted on average 124 ± 91 min (mean \pm SD, $n = 53$; range, 40–541 min), whereas under control conditions, average mitosis duration was 62 ± 8 min from cell rounding to cytokinesis (mean \pm SD, $n = 12$; range, 47–78 min). This prolongation is statistically significant ($P < 0.01$, Mann-Whitney *U* test).

The second major phenomenon, seen in the TTF-treated melanoma cultures, was that one-fourth of cells undergoing mitosis were destroyed as the formation of the cleavage furrow approached complete cell separation. During this process, the cell membrane ruptured, and many small membrane blebs formed, resembling post-mitotic apoptotic cell death (13). Two exemplary cells undergoing such destruction are shown in Fig. 3, B and C. Destructive effects were observed only in mitotic cells, whereas quiescent cells remained morphologically and functionally intact.

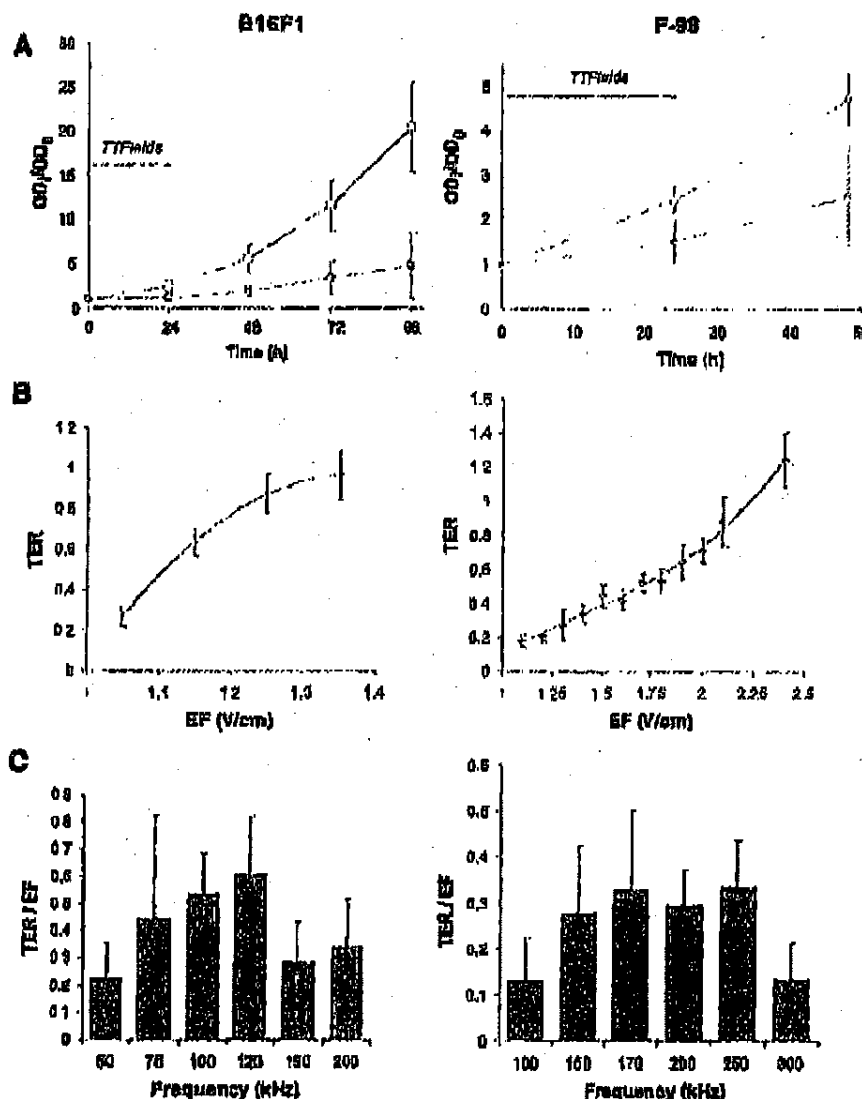
The third phenomenon, seen only in TTF-treated cultures, was nuclear rotation. In early mitosis, after cell rounding, nuclei could be seen rotating within the cell. A full rotation lasted on average 15 min. This effect resembles the whole-cell rotation previously described during exposure to intermediate-frequency alternating electric fields (7, 8).

A fundamental characteristic of electric fields is that at any point in space, they have a defined orientation corresponding to the direction of the force they exert on charges and polar elements. With regard to the latter, the force exerted by the field is maximal when the dipole is oriented in the direction of the field. With regard to the above, there are two main structural differences between quiescent and dividing cells. One is that the latter contain highly polar, spatially oriented microtubules and that they develop a discoidal, hourglass-shaped cell morphology during the cytokinesis phase. In view of these facts, one may expect that the electric field forces will have maximal effect

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Fig. 2. Time, field frequency, and intensity dependence of the effect of TTFs on malignant melanoma (B16F1, left column) and glioma cell (F-98, right column) proliferation. A, the number of cells in untreated cultures (control □) as compared with cultures treated with TTFs (■). The number of cells at each time point (OD) was normalized by the number of cells in the culture before initiation of treatment (OD₀). The number of control cells is seen to roughly double every 24 h throughout the experiment. TTFs were applied for 24 h continuously (solid line) at 100 kHz in the melanoma cultures and at 200 kHz in the glioma cultures. The increase in the number of treated melanoma (left) and glioma (right) cells over time is significantly smaller than control cells ($P < 0.001$). B, the effect of 24-h exposure to TTFs of increasing intensities. The magnitude of the effect is expressed using the TER. The inhibitory effect of the TTFs on proliferation increases with intensity in both cell types. Complete proliferation arrest (TER = 1) is seen at 1.33 and 2.23 V/cm in melanoma and glioma cells, respectively. C, change in the melanoma (left) and glioma (right) growth rate after 24 h of exposure to TTFs of different frequencies is normalized to the field intensity (TER/EF). A window effect is seen with maximal inhibition by TTFs at 120 kHz in melanoma cells and at ~200 kHz in glioma cells. Data are mean ± SE.



on the mitotic process when it is oriented along the lines of force of the field. To investigate this point, we fixed melanoma cell cultures and stained them with toluidine blue, immediately after 24 h of TTF treatment, to demonstrate mitoses and to distinguish vital from damaged or dead cells. The live and damaged mitotic cells (at the time of fixation) were grouped according to the orientation of their cleavage axis relative to the electric field direction. The cells were counted separately in each of four equal sectors that form angles of 0°, 45° (two sectors, 45 and 135), and 90° relative to the field direction. As seen in Fig. 4A, the live cells were randomly distributed in all sectors. In contrast, a much higher proportion of the damaged cells had their axis of division oriented along the field: 56% at 0° versus an average of 15% in each of the other orientations. Surprisingly, the number of cells per unit area in the two 45° sectors was found to be one-half that in the 0° sector. This finding may serve as an indication of an additional effect of TTFs: orientation of the cell division in the field direction. The cells in each of the above spatially oriented defined groups were further divided according to stages of mitosis at the time of fixation. At all stages, a higher fraction of damaged cells

had their axis of division oriented along the field. Moreover, 74% of the parallel oriented cells were damaged while being in metaphase (Fig. 4B).

The spatially organized mitotic spindle, which forms in dividing cells, consists of microtubules that have very large electric dipole moments (14) and may therefore be disoriented by the forces of the electric fields (13, 16). Actin filaments are also polar, however, they have no defined spatial orientation within the cells and are therefore not expected to be significantly affected by the fields. This prompted us to test whether TTFs disrupt mitosis by interfering with the normal formation, orientation, and movement of microtubules as compared with actin filaments as follows: Melanoma cell cultures were treated with TTFs for 24 h. After treatment, the cells were fixed, stained with monoclonal antibodies directed against microtubules and actin filaments, as well as for DNA, and thereafter studied with fluorescence microscopy (see "Materials and Methods"). In control cultures, 95% of cells undergoing mitosis exhibited the normal stages of mitosis with intact mitotic spindles. However, in TTF-treated cultures, more than one-half of the mitoses were abnormal,

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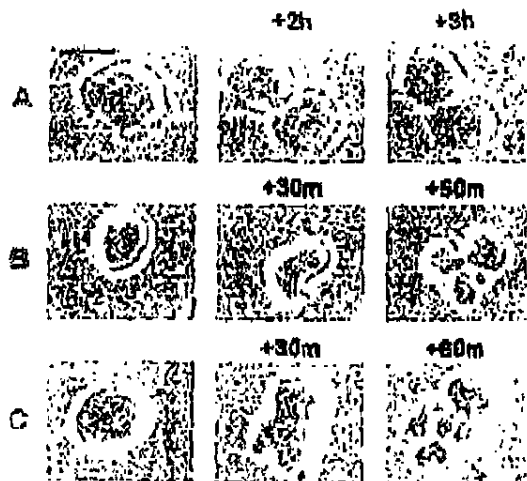


Fig. 3. Translucent microphotography of malignant melanoma cells exposed to TTFields. A, an example of a cell in mitosis treated by TTFields. Contrast to normal mitosis, the duration of which is less than 1 h, the depicted cell is seen to be stationary at metaphase for 3 h. B and C, two examples of the integration of TTFields-treated cells during cytokinesis. These consecutive images are shown: cell condensing (left), formation of the cleavage furrow (middle), and cell disintegration (right). Scale bar = 100 μ m.

Fig. 3 shows examples of the different forms of abnormal mitosis seen under TTField treatment. These included polyploid cells in prophase, III-segmented, multi-axial and single-spindled cells in metaphase, asymmetric anaphases, and a large proportion of cells in telophase (> 30%) with rosette shaped chromatinome assemblies. The normal and abnormal stages of mitosis in control and TTField-treated cultures are summarized and compared in Fig. 5G. In general, these abnormalities may serve as an indication of interference of TTFields with the normal behavior of the microtubules. In contrast, staining for actin filaments showed no difference between TTField-treated and control cultures.

Effect of TTFields on Tumors in Vivo. To test whether TTFields are effective in destroying tumor cells *in vivo*, we tested their effect on two animal tumor models: C57BL/6 mice inoculated intradermally with malignant melanoma cells (B16F1) and BALB/c mice inoculated intradermally with adenocarcinoma cells (CT-26). TTFields were generated between implanted (intradermal) wholly insulated wires placed on both sides of the tumor (see Fig. 1B). Mice with implanted electrodes were treated for 3–6 days continuously beginning 1 day after cell line inoculation. We found that 100–200 kV of TTFields at low intensities of <2 V/cm effectively inhibited malignant melanoma growth compared with the growth of non-treated control tumors. Photographs of examples of treated and non-treated malignant melanoma tumors are given in Fig. 6 for comparison. Treated tumors were significantly smaller than control tumors at the end of treatment (average treated tumor size was 47% of control tumor size; $n = 78$ mice, $P < 0.001$; Student's t test). Histopathological analysis of treated tumors showed extensive necrosis with aggregations of keratinic and basophilic debris (Fig. 6A). To test whether TTFields are effective on different tumor types, BALB/c mice with intradermal adenocarcinoma were treated with the same field parameters. Photographs of examples of such a treated and a non-treated adenocarcinoma tumors are provided for comparison in Fig. 6B. The average effect of TTFields on adenocarcinoma carrying mice was less dramatic than that seen for malignant melanoma (average treated tumor size was 73% of control tumor size at the end of treatment; $n = 14$ mice). After treatment, the tumors and their adjacent tissues were fixed, stained with H&E, and analyzed histopathologically. No change to the surrounding tissues was detected.

DISCUSSION

In this study, we have shown that when properly tuned, very low-intensity, intermediate-frequency electric fields (TTFields) stunt the growth of cancerous cells. We have demonstrated this inhibitory effect in all proliferating cell types tested, whereas, nonproliferating cells and tissues were unaffected. Interestingly, different types of cancerous cells showed specific intensity and frequency dependences of TTField inhibition. We have demonstrated that two main processes occur at the cellular level during exposure to TTFields: arrest of proliferation and cell destruction. The damage caused by TTFields to these replicating cells was shown to be dependent on the orientation of the division process in relation to the field vector, indicating that this effect is nonthermal. Indeed, temperature measurements made within culture dishes during treatment and on the skin above treated tumors *in vivo*, showed no significant elevation in temperature compared with control cultures/mice. Also, TTFields caused the dividing cells to orient in the direction of the applied field in a manner similar to that described in cultured human cervical epithelial cells exposed to constant electric fields (17). At the subcellular level, we have found evidence indicating that TTFields disrupt the normal polymerization-depolymerization processes of microtubules during mitosis. Indeed, the described abnormal mitotic configurations seen after exposure to

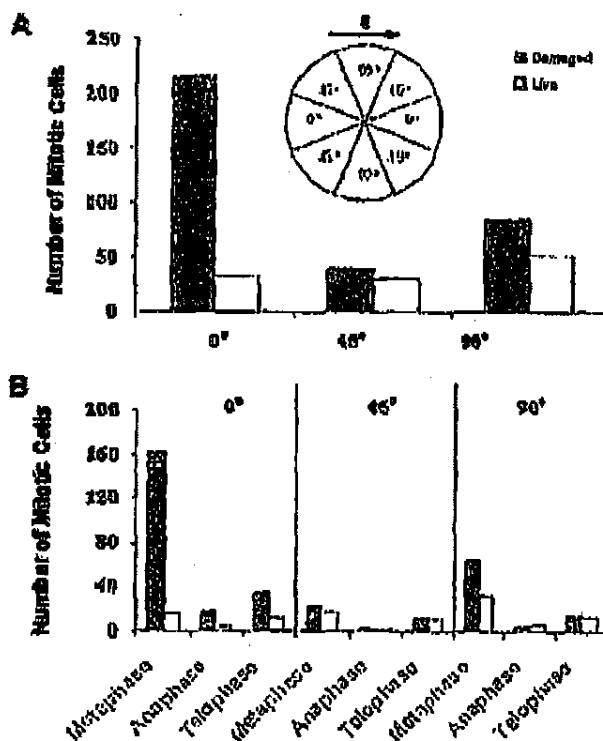


Fig. 4. Dependence of TTFields-induced cellular damage on the orientation of cell division relative to field direction. Graphs represent the number of mitotic cells counted in time TTField-treated malignant melanoma cultures (100 kV). A, total number of damaged (■) and alive (□) cells in each of three sectors of different angles relative to the field direction (inset). The number of damaged cells is more than 5-fold higher than the corresponding number of the cells when division is aligned at or close to 0° relative to the electric field direction. In sectors of other angles, the number of damaged cells only slightly exceeds the live ones. Note that because the 45° sector is double that of each of the other two sectors, the number of cells observed in this orientation was twice. B, dividing cell orientation at 0° in the electric field. The number of damaged cells (■) is significantly larger than that of non-damaged cells (□) at all three phases of mitosis. However, the highest number of damaged cells in this orientation is seen at telophase (twice more than metaphase).

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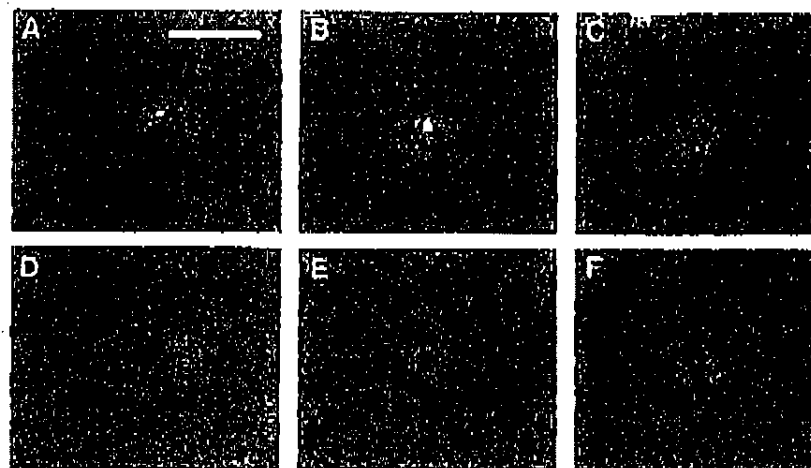
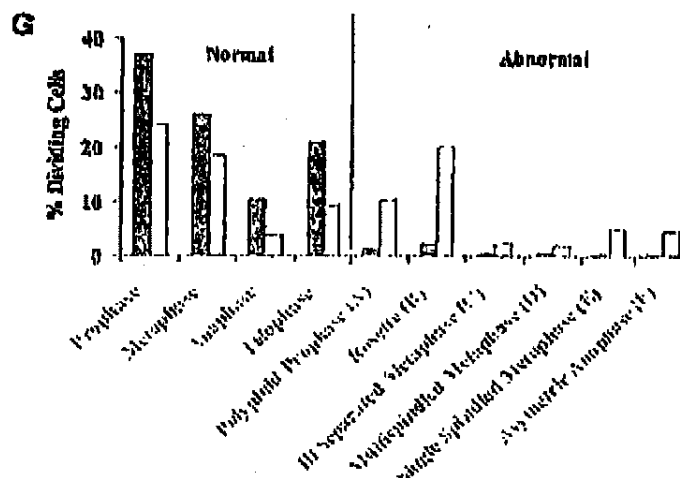


Fig. 5. Immunohistochemical staining of abnormal mitotic figures in TTF fields-treated sarcoma. Malignant melanoma cells (a - d) were treated for 24 h at 100 kHz and then stained with monoclonal antibodies for microtubules (green), actin (red), and DNA (blue). The photomicrographs show abnormally abnormal mitotic including: polyploid metaphase (A); eosinophilic (B); disorganized metaphase (C); multiphase mitotic phase (D); single-spindle mitotic phase (E); and non-symmetrical mitotic phase (F). G, the percentage of treated (□) and control (■) mitotic cells in each of the normal and abnormal phases of mitosis.



TTF fields are similar to the morphological abnormalities seen in cells treated with agents that interfere directly (18, 19) or indirectly (20-22) with microtubule polymerization (e.g., Taxol).

To explain how TTF fields cause orientation-dependent damage to dividing cancerous cells and disrupt the proper formation of the mitotic spindle, we modeled the forces exerted by TTF fields on intracellular charges and polar particles using finite element simulations (see "Materials and Methods"). We identified two main mechanisms by means of which the electric fields may affect dividing cells. The first relates to the field effect on polar macromolecule orientation. Within this framework, during the early phases of mitosis, i.e., in pre-telophase, when tubulin polymerization-depolymerization drives the proliferation process, the electric field forces any tubulin dimers, positioned further than 14 nm away from the growing end of a microtubule, to orient in the direction of the field (Fig. 7A). This force moment, (10^{-8} pN) acting on the dimers, is sufficient to interfere with the proper process of assembly and disassembly of microtubules that is essential for chromosome alignment and separation (23). This effect can explain the mitotic arrest of TTF field-treated cells (24). The second mechanism, which interferes with cell division and is most likely to play an important role in cell destruction, becomes dominant during cleavage. As seen in the simulations depicted in Fig. 7B, the electric field within quiescent cells is homogenous, whereas the field inside mitotic cells, during cytokinesis, is not homogenous. We see an

increased field line concentration (indicating increased field intensity) at the furrow, a phenomenon that highly resembles the focusing of a light beam by a lens. This inhomogeneity in field intensity exerts a unidirectional electric force on all intracellular charged and polar entities, pulling them toward the furrow (regardless of field polarity). For example, for a cleavage furrow that reached a diameter of 1 μ m in an external field of only 1 V/cm, the force exerted on the microtubules is in the order of 5 pN. This magnitude is compatible with the reported forces necessary to stall microtubule polymerization that is 4.3 pN (25). With regard to other particles such as cytoplasmic organelles, they are polarized by the field within dividing cells. Once polarized, the forces acting on such particles may reach values up to an order of 60 pN resulting in their movement toward the furrow at velocities that may approach 0.03 μ m/s. At such velocity, cytoplasmic organelles would pile up at the cleavage furrow within a few minutes, interfering with cytokinesis and possibly leading to cell destruction. We also found that the electric forces acting on intracellular particles are maximal when the axis of division is aligned with the external field. This is consistent with the dependence of the destructive effect of TTF fields on the angle between division axis and the field (Fig. 4). In addition, the calculated dependence of the magnitude of this force on frequency (data not shown) is consistent with the experimentally determined frequency dependence of the

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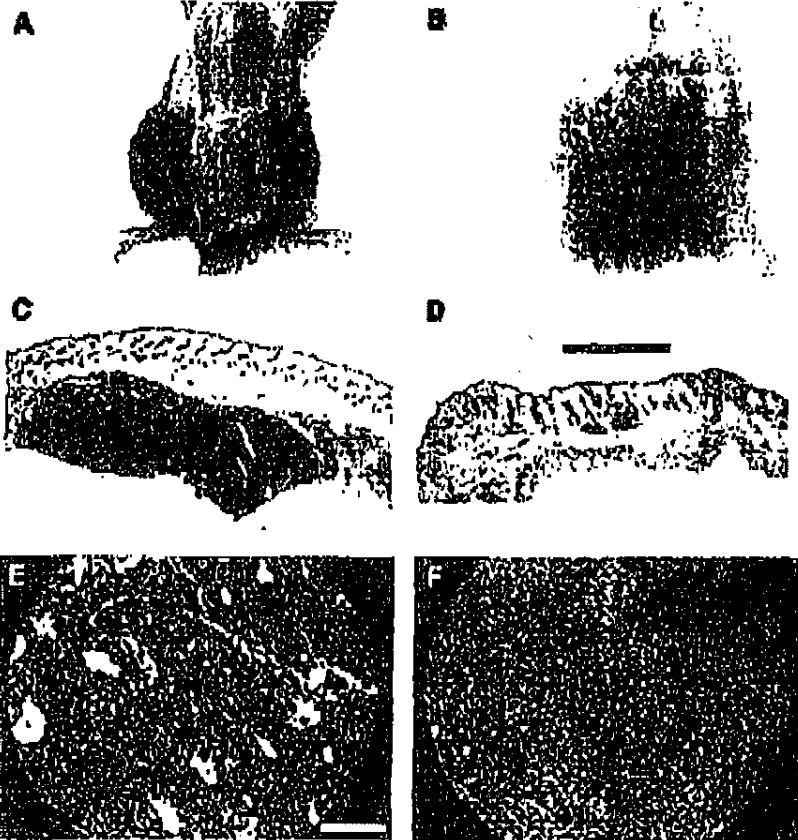


Fig. 6. *In vivo* effects of TTFs on melanoma and adenocarcinoma. (A) and (B) gross tumor specimens. (C) and (D) histological sections of TTF-treated and untreated melanomas. (E) and (F) histological sections of melanoma cells. (A) and (B) show gross tumor specimens. (C) and (D) show histological sections of TTF-treated and untreated melanomas. (E) and (F) show histological sections of melanoma cells. (A) and (B) show gross tumor specimens. (C) and (D) show histological sections of TTF-treated and untreated melanomas. (E) and (F) show histological sections of melanoma cells.

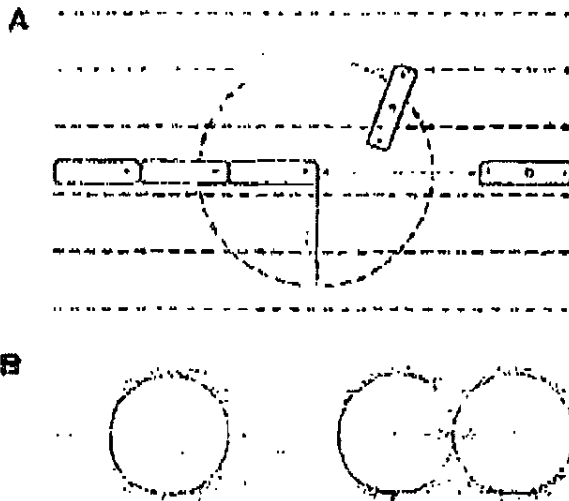


Fig. 7. A schematic representation of two tubular sheath electrodes near the tip of an elongating microtubule in a dividing cell. The force that a 1-V/cm uniaxial TTF field exerts on a tubule is shown. The force is less than 14 mN away from the microtubule (a) is smaller than the force exerted by the polar microtubule tip, and therefore it will align according to the field generated by the microtubule. In contrast, filaments further than 14 mN from the end of the microtubule (b) are aligned by the force of the TTF field (aligned filaments) in a direction that may not be compatible with the polymerization step dynamics process. B. Schematic representation of the effect of force of the electric field on a dividing cell (left) and a cell undergoing mitosis (right). The diameter of the cell in the microtubule was 10 μ m and microtubule diameter 3 μ m. From the microtubule, the electric field is initially uniform (right) and then between the tips of the filaments. In the dividing cell, the field is "inhomogeneous" - the field intensity (line density) increases toward the cleavage furrow.

Inhibitory effect of TTFs on melanoma and glioma cell proliferation (Fig. 2C).

In conclusion, we have demonstrated that TTFs inhibit both the proliferation of malignant cells in culture and the growth of tumors in mice while showing no general side effects or local histopathological damage. The mechanism of action of the fields is, at least in part, dependent on disruption of the microtubules of the mitotic spindles and the electric forces resulting from focusing of the field in the dividing cells. The highly specific effects of these fields on dividing cells, together with the relative ease of applying them, focusing them, and screening from them, make them an attractive candidate to serve as a novel treatment modality for cancer.

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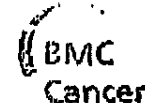
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RESEARCH ARTICLE

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TTFields alone and in combination with chemotherapeutic agents effectively reduce the viability of MDR cell sub-lines that over-express ABC transporters

Rosa S Schnelderman^{1†}, Esther Shmueli¹, Eilon D Kirson¹ and Yoram Palti^{1,2}

Abstract

Background: Exposure of cancer cells to chemotherapeutic agents may result in reduced sensitivity to structurally unrelated agents, a phenomenon known as multidrug resistance (MDR). The purpose of this study is to investigate cell growth inhibition of wild type and the corresponding MDR cells by Tumor Treating Fields - TTFields, a new cancer treatment modality that is free of systemic toxicity. The TTFields were applied alone and in combination with paclitaxel and doxorubicin.

Methods: Three pairs of wild type/MDR cell lines, having resistivity resulting from over-expression of ABC transporters, were studied: a clonal derivative (C1T) of parental Chinese hamster ovary AAG cells and their etoposide-resistant sub-line Emt6; human breast cancer cells MCF-7 and their mitoxantrone-resistant sub lines MCF-7/Mx and human breast cancer cells MDA-MB-231 and their doxorubicin resistant MDA-MB-231/Dox cells. TTFields were applied for 72 hours with and without the chemotherapeutic agents. The numbers of viable cells in the treated cultures and the untreated control groups were determined using the XTT assay. Student t-test was applied to assess the significance of the differences between results obtained for each of the three cell pairs.

Results: TTFields caused a similar reduction in the number of viable cells of wild type and MDR cells. Treatments by TTFields/drug combinations resulted in a similar increased reduction in cell survival of wild type and MDR cells. TTFields had no effect on intracellular doxorubicin accumulation in both wild type and MDR cells.

Conclusions: The results indicate that TTFields alone and in combination with paclitaxel and doxorubicin effectively reduce the viability of both wild type and MDR cell sub-lines and thus can potentially be used as an effective treatment of drug resistant tumors.

Background

Multidrug resistance (MDR) [1] is encountered when cancer cells are exposed to chemotherapeutic agents for a few replication cycles. It is manifested in reduced sensitivity to both the specific chemotherapy as well as to a number of structurally unrelated agents. This phenomenon obviously poses a serious impediment to successful chemotherapy. Three decades of multidrug resistance research have identified a number of mechanisms by

means of which cancer cells elude the effects of chemotherapeutic agents. The most often encountered MDR is the one resulting from over-expression of ATP-binding cassette transporters such as P-glycoprotein (MDR1), multidrug resistance-associated protein-1 (MRP1), and the breast cancer resistance protein (BCRP) [1-8]. These transporters, that recognize substrates of diverse chemical nature, lower the intracellular concentration of these substrates and are normally involved in detoxification [4,5].

MDR can potentially be overcome by the use of anti-tumor modalities that are not involved in membrane transport, for example, anti-angiogenic agents and physical

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modalities such as radiotherapy, heat and electric fields. Different types of electric fields were reported to inhibit cancer cell proliferation and cause cancer cell destruction, for example: exposure of cancer cells to low amplitude DC currents [6], low intensity, low frequency (50 Hz) AC currents [7] and the intermediate frequency (100-300 kHz) alternating electric fields, termed TFields [8-12].

TFields are a new physical cancer treatment modality that has recently been demonstrated to be highly effective when applied to cell cultures, animal cancer models, as well as patients suffering from locally advanced and/or metastatic solid tumors [8-12]. TFields are alternating electric fields of low intensity (1-3 V/cm) and intermediate frequency (100 - 800 kHz) that are generated by special insulated electrodes applied to the skin surface. These specially tuned fields have no effect on quiescent cells while having an anti-proliferation and destructive effect on mitotic cells. This effect is due to the fact that during cytokinesis, TFields exert forces that move charged or polar macromolecules and organelles towards the narrow neck, separating the newly forming daughter cells [8,9]. They also interfere with the polymerization processes of the microtubule spindle during cell division. Thus, TFields disrupt the cell structure, inhibit cell division and result in cell death. In contrast to most anti-cancer agents, TFields are not associated with any meaningful systemic toxicity [9-12]. Furthermore, it was recently shown that TFields may be used clinically, not only as an anti-proliferation agent but also as effective adjuvant to currently used chemotherapeutic agents [9].

In view of the above, the target of the present study was to test the possibility of using TFields for treating multi-drug resistant cancerous and non cancerous cell lines, both as a standalone treatment and in combination with chemotherapy.

Methods

Materials

All cell culture media, serum and media supplements were obtained from Biological Industries, Beth Haemek, Israel. All drugs and chemical agents were obtained from Sigma.

Cell lines

The following cell lines and their drug resistant derivatives were used: A clonal derivative (C11) of parental Chinese hamster ovary A48 cells and their cisplatin-resistant sub-lines Emt^R cells having ATP dependant MDR1 type drug resistance [13], a kind gift from Prof. G. Eytan Dept. of Biology, Technion, Haifa, Israel; Human breast cancer wild type MCF-7 cells, obtained from ATCC and their mitoxantrone-resistant sub-lines MCF-7/Mx having ABCG2 transporter [14], a kind gift from Prof. M. Liaco-

vitch, Dept. of Biological Regulation Weizmann Institute of Science, Rehovot, Israel; Human breast cancer wild type MDA-MB-231 cells obtained from ATCC and from which doxorubicin resistant MDA-MB-231/Dox cells were developed in our laboratory using a stepwise increase in drug concentration protocol. This procedure is identical with that developed for these cells in other laboratories [15] for inducing MDR1 type of ABC transporters. The A48/Emt^R cell lines were maintained as a monolayer in minimal essential medium containing 5% fetal calf serum, 2 mM glutamine, 100 units/ml penicillin G, and 100 µg/ml streptomycin sulphate. The Emt^R cell medium also included 1 µM of emetine. The MCF-7/MCF-7/Mx and MDA-MB-231/MDA-MB-231Dox cell lines were maintained under monolayer conditions in DMEM containing 10% fetal calf serum, 2 mM glutamine, 100 units/ml penicillin G, and 100 µg/ml streptomycin sulphate. The MCF-7/Mx cell medium also included 250 nM of mitoxantrone and the MDA-MB-231/Dox cells medium also included 0.1 µM of doxorubicin.

All cells were kept in a 5% CO₂ incubator at 37°C. Exponentially growing cells were passaged twice a week using a standard trypsinization procedures.

Cytotoxicity assay

The level of resistance to doxorubicin and paclitaxel was determined by means of the XTT assay as previously described [8,9]. Briefly, 2×10^4 cells/well were plated in 24-well plate (NUNC), incubated without drugs for 24 h and then the initial number of cells, OD₀, was determined following incubation of with the XTT reagent using ELISA Reader (TECAN Sunrise, USA). The medium was then exchanged with ones containing different drug concentrations, 4 wells for each drug concentration (doxorubicin: 0.001-100 µM; paclitaxel: 0.0001-100 µM). After 72 h, the culture media was discharged, XTT reagent was added and the final cell number, OD_{72 h}, was determined. Data obtained from 3 - 5 experiments were collected and the mean values and standard deviations (SEM) of OD_{72 h}, representing final number of viable cells, were calculated for each drug concentration. Cell survival was presented as percentage of viable cells as compared to the corresponding viable cell number in no - drug controls. Drug concentrations inhibiting cell growth by 50% (IC₅₀) were calculated from relative survival curves using the median-effect principle [16].

Exposure to TFields

As previously described [9,11], two pairs of electrodes, insulated by a ceramic having a very high dielectric constant (NovoCure Ltd, Haifa, Israel), were positioned at 90° with respect to each other in both treatment and control Petri dishes. The distance between the electrodes in each

pair was 20 mm. Each pair of electrodes was alternatively connected for 250 ms to a sinusoidal waveform generator (NovoTTF, NovoCure Ltd. Haifa, Israel) that produced 1.75 V/cm, 150 kHz fields in the medium [8]. The 150 kHz frequency of TTFs was found to be effective for treatment of all cells studied.

Four different sets of conditions in each experiment were conducted for each cell line in conjunction with each chemotherapeutic agent: untreated control cells, cells treated by the chemotherapeutic agent alone, cells exposed to TTFs, and cells having a combined TTFs - Chemo exposure (8 Petri dishes for each condition). After 72 h, the culture media was discharged, XTT reagent was added and the final number of viable cells, OD_{72h} , was determined. Data obtained from 3 - 5 experiments were collected and the mean values and standard deviations (SEM) of OD_{72h} , representing final viable cell numbers were calculated for each set of conditions. Cell survival was presented as percentage of viable cells out of the corresponding viable cell number in untreated controls. Student t-test was applied to assess the significance of the differences between results obtained for each of the four conditions tested. In order to assess the extent of possible chemotherapeutic dose reduction when applied in combination with TTFs, dose reduction indexes (DRI) for each TTFs/drug combination were calculated according to [17].

The DRI for the same level of effect (DRI_m) was calculated as the ratio of the concentration of drug alone to that of the combined drug-TTFs treatment:

$DRI_m = D_{\text{drug alone}} / D_{\text{combined treatment}}$. The DRIs determine the magnitude of dose reduction allowed for each drug when given in combination with TTFs, as compared with the agent dose that achieves the same level of effect. DRI values larger than 1 indicate increased sensitivity to the drug.

Intracellular Doxorubicin Accumulation

The intracellular accumulation of doxorubicin was determined for both wild type and drug resistant sub-lines. Cells were grown in total 16 Petri dishes (35 mm, NUNC) as monolayers for 24 h in drug-free medium and then incubated for 1 h in the absence or presence of doxorubicin with or without exposure to TTFs (1.75 V/cm, 150 kHz) (4 Petri dishes for each treatment condition). The cells were washed with ice cold PBS three times and solubilised with 100 μ l of 2% SDS. The solutions were then transferred to black 96-well plates (NUNC) and doxorubicin fluorescence was measured by spectrofluorometry (ELISA Reader TECAN F-200) at λ_{em} 600 nm and λ_{ex} 450 nm. Data obtained from 2 - 4 experiments were collected and the mean values and standard deviations (SEM) of doxorubicin fluorescence were calculated for each condi-

tion. Student t-test was applied to assess the significance of the differences between results obtained for each of the three cell pairs.

Results

Effect of TTFs on wild type cells and their MDR sub-lines
In order to study the TTFs effect, field intensities that reduce the WT cell survival by about 50% were used. A comparison between the survival of wild type and MDR cells, when exposed to such TTFs, is given in Figure 1. The reduction in the number of viable cells is seen to be very similar (48-61% of control) in all wild type and paired MDR lines. In other words, the drug resistant cell lines have about the same sensitivity to TTFs as their corresponding wild type cell lines.

Exposure to doxorubicin or paclitaxel in combination with TTFs

Figure 2 compares between the cytotoxicity-dose curves of chemotherapeutic agents (paclitaxel and doxorubicin) of wild type cells and MDR sub-lines. It is seen that the resistivity of the MDR sub-lines is manifested in a significant right shift of the drug cytotoxicity-dose curves. As a result of these shifts the calculated IC_{50} values (Table 1) for doxorubicin and paclitaxel, for all pairs of WT-MDR cell lines studied, give very high IC_{50} ratios (resistance index RI): 55 - 79 for doxorubicin and 128 - 653 for paclitaxel.

A comparison between cell viability following separate and combined TTFs/drug exposures are presented in Figure 3. It is seen that in all combined exposures cell survival is lower as compared with exposure to any of the

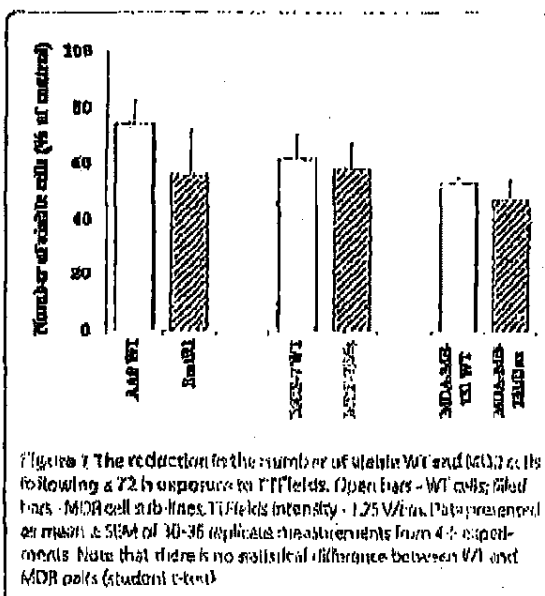
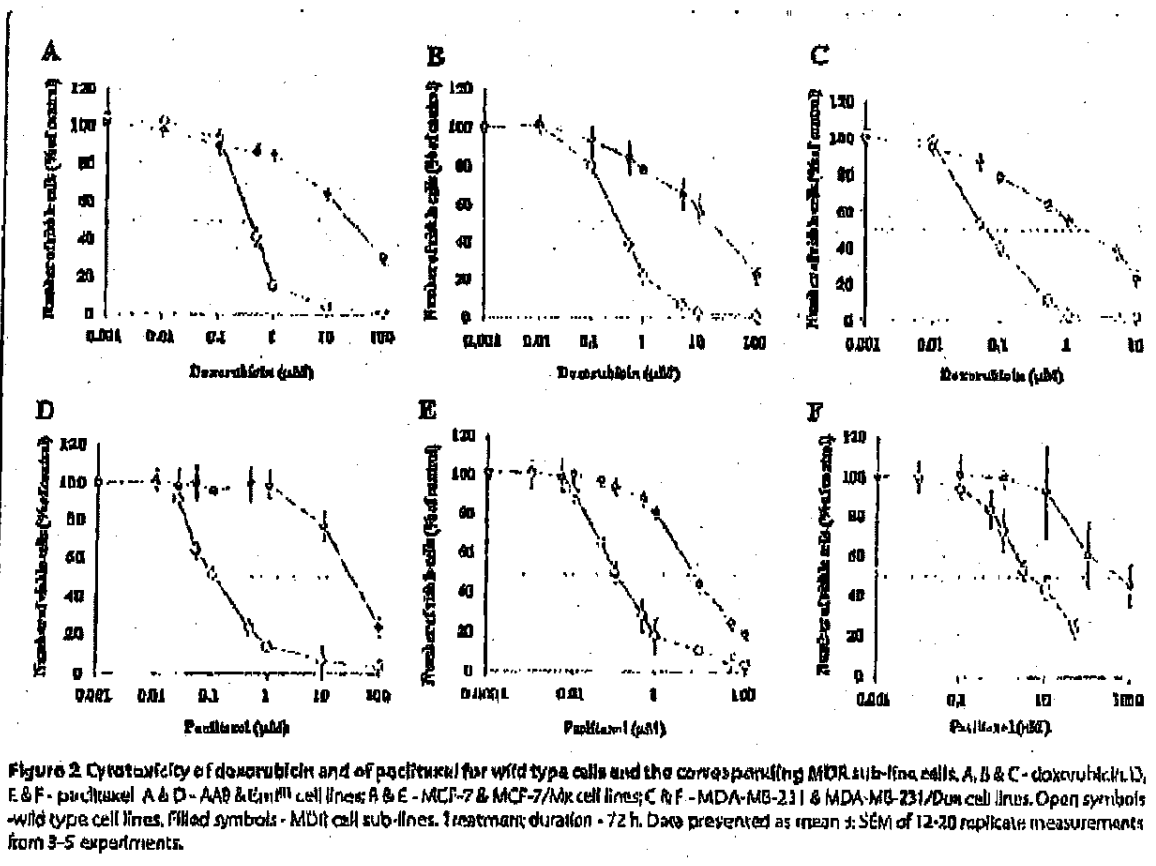


Figure 1 The reduction in the number of viable WT and MDR cells following a 72 h exposure to TTFs. Open bars - WT cells; filled bars - MDR cell sub-lines. TTFs intensity - 1.75 V/cm. Data presented as mean \pm SEM of 30-35 replicates from 4 experiments. Note that there is no statistical difference between WT and MDR cells (Student t-test).



chemical agents (doxorubicin or paclitaxel) or TTFields alone (see Figure 1). Moreover, the cell survival of the MDR sub-lines and WT cell lines, when subjected to the combined exposure is similar, i.e. the resistivity or reduced drug sensitivity of MDR cells are not evident under these conditions.

Table 2 summarizes the combined treatment efficacy for MDR cells (see Figures 2 & 3) expressed in terms of Dose Reduction Index (DRI). TTFields are seen to increase the sensitivity to doxorubicin of all three MDR sub-lines by at least two orders of magnitude. The corre-

sponding increase for paclitaxel is even greater, i.e. two to three orders of magnitude. In other words, the efficacy of combined drug/TTFields treatment of MDR cells greatly exceeds that of treatment with drug alone.

Intracellular Doxorubicin Accumulation

An inherent feature of overexpressed ABC transporters phenotype is the reduction in cell uptake of doxorubicin due to its exclusion [18]. The ability of MDR cells to exclude doxorubicin was determined by means of spectrofluorometric analysis. Figure 4A illustrates the intrac-

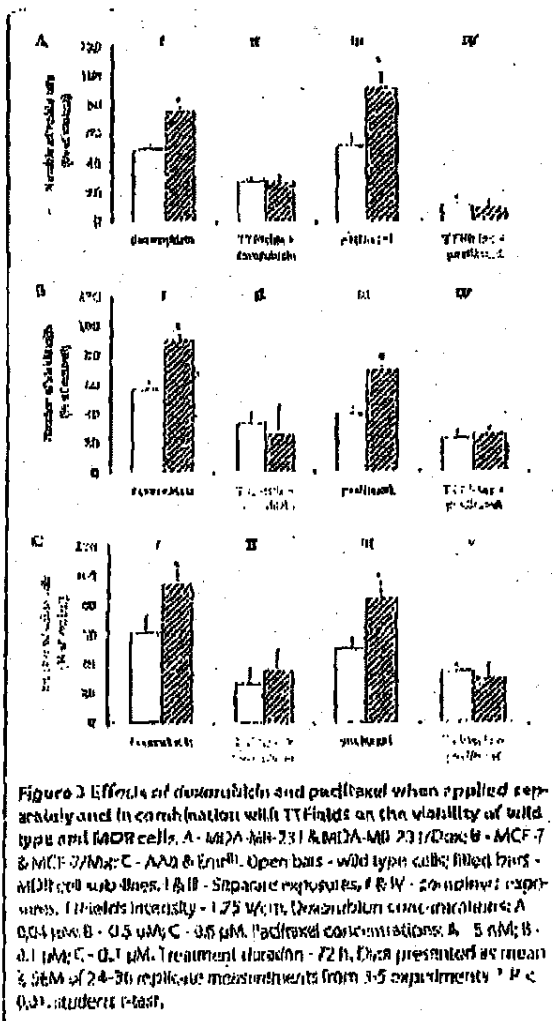
Table 1: IC₅₀ values for doxorubicin and paclitaxel

| Drug | IC ₅₀ | | | | | |
|------------------|------------------|------|-------|----------|------------|----------------|
| | AAB | Emr1 | MCF-7 | MCF-7/Mx | MDA-MB-231 | MDA-MB-231/Dox |
| Doxorubicin (μM) | 0.6 | 48.4 | 0.5 | 30.8 | 0.04 | 2.2 |
| Paclitaxel (μM) | 0.1 | 63.3 | 0.09 | 9.9 | 0.003 | 0.829 |

Drug concentrations inhibiting cell growth by 50% (IC₅₀) were calculated from relative survival curves (see Figure 2) using the median-effect principle [15].

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intracellular concentration of doxorubicin in AA8 (WT) and Emr1 (MDR) cell lines as a function of extracellular doxorubicin concentration with and without exposure to TTFields. As the drug is partially excluded from drug resistant sub line, the relative intracellular doxorubicin concentration in Emr1 cells is lower by 44.9, 49.7 and 49.6% at 15, 80 and 45 μ M extracellular doxorubicin concentration respectively, as compared with the wild type cells (Figure 4A, open symbols). Exposure of AA8 (WT) and Emr1 (MDR) cell lines to TTFields during incubation with doxorubicin had no effect on the intracellular concentration of the drug in both wild type and drug resistant sub lines indicating that TTFields affect neither doxorubicin uptake nor its exclusion (Figure 4A, filled symbols). Figure 4B depicts doxorubicin accumulation by MDR sub lines relative to the corresponding WT cell

Table 2: Dose reduction indexes for MDR cell sub-lines treated alone and in combination with TTFields.

| Drug | Dose reduction index (DRI) | | |
|-------------|----------------------------|----------|----------------|
| | Emr1 | MCF-7/Mx | MDA-MB-231/Dox |
| Doxorubicin | 105 | 195 | 250 |
| Paclitaxel | 815 | 4404 | > 10,000 |

The DRI estimates the extent to which the dose of one or more agents in the combination can be reduced to achieve effect levels that are comparable with those achieved with single agents. The effect of TTFields/drug combined treatment for each MDR cell sub-line was as shown in Figure 3. The same effect of single drug was obtained from dose-response curves (see Figure 2). The DRI was calculated as a ratio of drug concentrations used alone vs. drug concentrations used in combination with TTFields.

lines exposed to 30 μ M of doxorubicin with and without TTFields. The relative intracellular doxorubicin concentration is lower by $49.7 \pm 5\%$ for Emr1, $66.4 \pm 5\%$ for MCF-7/Mx and by $32.6 \pm 6\%$ for MDA-MB-231/Dox as compared with the corresponding wild type cells (Figure 4A, open bars). TTFields have no effect on intracellular doxorubicin concentrations in all wild type and drug resistant cell lines (Figures 4B, filled bars).

Discussion

ABC transporters provide vital protection from foreign compounds by exporting these compounds from the cell, thus lowering their intracellular concentration. Unfortunately, exposure of cancer cells to chemotherapeutics, mainly during relapse treatment, causes transporter upregulation such that the resulting over-expression of ABC transporters becomes one of the main causes of treatment failure. Moreover, various tumors such as renal cell, adrenocortical, colon and hepatocellular cancers express ABCB1 and are practically chemoresistant [19]. To overcome this problem chemosensitizers that block ABC transporter-mediated efflux were developed and have been used to combat MDR. However, this approach has not been clinically successful and therefore novel approaches that bypass, rather than block ABC transporters, are being sought for [20]. As the TTFields do not affect drug transport (see Figure 4) they fall into this category.

The results of this study clearly indicate that both the MDR and WT cells are similarly sensitive to TTFields. Moreover, TTFields were shown to enhance MDR cell sensitivity to chemotherapeutic agents, so as to equal that of WT cells under the same set of conditions (Figure 3). This phenomenon can only be partially explained on the basis of the corresponding dose-response curves (Figure 2) and the drug export rate (Figure 4). As demonstrated

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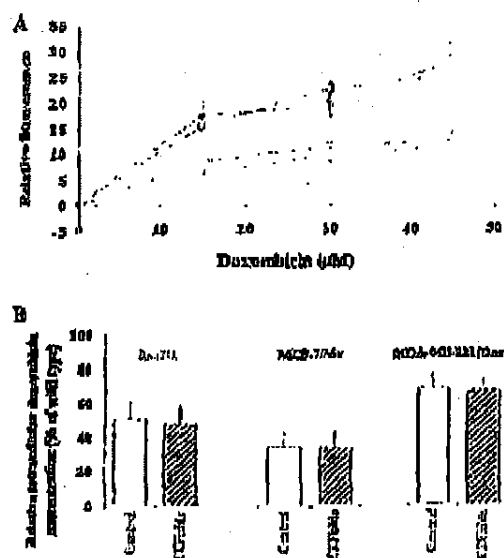


Figure 4 Effect of TTFields on doxorubicin accumulation. A - Dose response curve for A48 cells and for their MDR sub-line Lova. Open symbols - cells exposed to drug alone; filled symbols - cells exposed simultaneously to drug and TTFields. Circles - A48 cell line; squares - Lova sub-line. Intensity of TTFields - 1.75 V/cm, frequency - 150 kHz, treatment duration - 1 h. Data presented as mean ± SEM of 16-24 replicate measurements from 3-4 experiments. B - Effect of TTFields on doxorubicin accumulation by different MDR cell sub-lines relative to their parental wild type cell lines. Ordinate: relative intracellular doxorubicin concentration in the drug resistant sub-lines presented as % of the corresponding concentration in the wild type cells. Open bars - cells exposed to drug alone; filled bars - cells exposed simultaneously to drug and TTFields. Doxorubicin concentration: 30 μM. TTFields intensity - 1.75 V/cm, TTFields frequency - 150 kHz. Treatment duration - 1 h. Data are presented as mean ± SEM of 12-24 replicate measurements from 3-4 experiments.

In Figure 5, the dose-response curve of the drug resistant cells is shifted to the right relative to the WT cells (see also Figure 2). The magnitude of the shift is such that the 50% inhibition of WT cells that is obtained at a concentration of 0.04 μM requires a concentration of 2.2 μM for the MDR sub-line, i.e. a 55 fold higher concentration. However, the data depicted in Figure 4 and corresponding reports for low doxorubicin doses [21] indicate that the drug export lowers the intracellular concentration only by a factor of about 2. This means that some other factor must be responsible for the MDR resistance that corresponds to additional 20-30 fold drug concentration change. From the data in Figure 3A we also learn that both the MDR and WT cells are similarly highly sensitive to combined chemotherapy - TTFields treatments. Thus, while a 50% inhibition of MDR cells by doxorubicin alone requires a concentration of 2.2 μM, the combined treat-

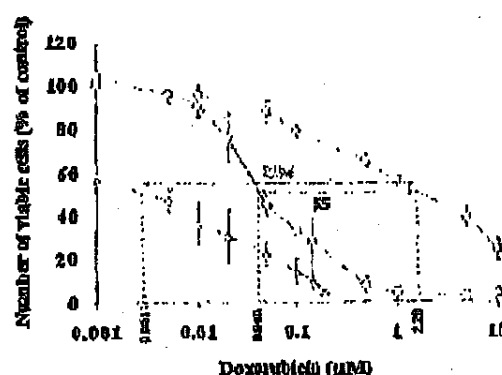



Figure 5 Effect of 72 h application of TTFields and chemotherapeutic agents, separately and in combination on the viability of MDA-MB-231 wild type cells and MDA-MB-231/Dox MDR cells. - O - MDA-MB-231 cells treated with doxorubicin alone; - Δ - MDA-MB-231 cells treated with doxorubicin in combination with TTFields (ref. [9]); - □ - MDA-MB-231/Dox cells treated with doxorubicin alone.

ment of TTFields and low concentration of doxorubicin (0.0017 μM) is sufficient to induce a similar inhibition. This is equivalent to an increased intracellular concentration of doxorubicin by a factor of over 1000. Thus, TTFields seem to have effects specific to MDR cells, not related to drug transport, that increase the MDR cell's sensitivity to chemotherapy. This conclusion is consistent with that of others [22-24] that attribute the MDR resistance, in addition to reduced drug uptake, to a number of potential mechanisms such as: sugar metabolism and energy production, alterations in cytoskeletal elements, microtubule and mitochondria distribution, etc. Within the framework of the above suggested mechanisms [22-24] it seems that the integrity of cytoskeleton and microtubule as well as the mitochondria distribution may be the most vulnerable to the forces produced by TTFields. The former may be disrupted by particle movements induced by the dielectrophoresis induced during TTFields application [8] while the latter are highly polar in themselves and are therefore directly subjected to the alternating field forces.

Conclusions

The results of this study support the notion that TTFields may be used, both as an effective stand alone anti-proliferation agent for MDR cells, as well as an effective adjuvant that enhances chemotherapy efficacy. Furthermore, since TTFields are a physical modality, their therapeutic efficacy is independent of interaction with cell receptors. Therefore their efficacy is not expected to be limited to a specific set of cell types [8-12]. On the basis of the above, we believe that there is a high probability that TTFields

BMC Medical Physics



Research article



Chemotherapeutic treatment efficacy and sensitivity are increased by adjuvant alternating electric fields (TTFields)

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Published: 8 January 2009

Received: 3 September 2008

BMC Medical Physics 2009, 9:1 doi:10.1186/1756-6649-9-1

Accepted: 8 January 2009

This article is available from: <http://www.biomedcentral.com/1756-6649/9/1>

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Abstract

Background: The present study explores the efficacy and toxicity of combining a new, non-toxic, cancer treatment modality, termed Tumor Treating Fields (TTFields), with chemotherapeutic treatment in-vitro, in-vivo and in a pilot clinical trial.

Methods: Cell proliferation in culture was studied in human breast carcinoma (MDA-MB-231) and human glioma (U-118) cell lines, exposed to TTFields, paclitaxel, doxorubicin, cyclophosphamide and dacarbazine (DTIC) separately and in combinations. In addition, we studied the effects of combining chemotherapy with TTFields in an animal tumor model and in a pilot clinical trial in recurrent and newly diagnosed GBM patients.

Results: The efficacy of TTFields-chemotherapy combination in-vitro was found to be additive with a tendency towards synergism for all drugs and cell lines tested (combination index ≤ 1). The sensitivity to chemotherapeutic treatment was increased by 1-3 orders of magnitude by adjuvant TTFields therapy (dose reduction indexes 23 - 1316). Similar findings were seen in an animal tumor model. Finally, 20 GBM patients were treated with TTFields for a median duration of 1 year. No TTFields related systemic toxicity was observed in any of these patients, nor was an increase in Tamoxifen toxicity seen in patients receiving combined treatment. In newly diagnosed GBM patients, combining TTFields with Tamoxifen treatment led to a progression free survival of 155 weeks and overall survival of 39+ months.

Conclusion: These results indicate that combining chemotherapeutic cancer treatment with TTFields may increase chemotherapeutic efficacy and sensitivity without increasing treatment related toxicity.

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Background

A new physical cancer treatment modality termed Tumor Treating Fields, or TTFields, has recently been demonstrated to be highly effective when applied to cell cultures, animal cancer models, as well as to patients suffering from locally advanced and/or metastatic solid tumors [1-3]. In a pilot clinical trial, the medians of time to disease progression and overall survival of recurrent GBM patients treated by TTFields alone were more than double the reported medians of historical control patients [1]. In contrast to the widely used physical treatment modality, ionizing radiation, TTFields are not associated with significant side effects.

TTFields are low intensity (1-2 V/cm), intermediate frequency (100 - 200 kHz) alternating electric fields generated by special insulated electrodes applied to the skin surface. These specially tuned fields have no effect on quiescent cells while having an anti-mitotic effect on dividing cells. During cytokinesis, TTFields generate non-uniform intracellular fields that exert forces that move polar macromolecules and organelles towards the narrow neck, separating the newly forming daughter cells, by a process termed dielectrophoresis. These molecular and organelle movements, together with an interference with the spindle tubulin polymerization process, inhibit cell division and lead to cell death [2]. Fortunately, the dividing cells of the hematopoietic system are not affected by TTFields as the muscles surrounding the marrow containing bones serve as an effective electric field shield. Moreover, due to their relatively high frequency range and very low intensity, TTFields do not stimulate nerves and muscles, do not generate meaningful temperature elevation or puncture the cell membrane (as the strong electroporation fields do [4]). Thus, TTFields are not associated with meaningful toxicity in contrast to most anti-cancer agents currently in use [5].

In view of the unfavorable therapeutic indexes of the available effective chemical and physical (i.e. ionizing radiation) therapeutic agents, many cancer treatment protocols require simultaneous or sequential use of a number of therapeutic agents in an attempt to increase efficacy while maintaining tolerable toxicity [5-7]. Within this framework it is generally accepted that by adding ionizing radiation [8] to chemotherapy one gets both the benefit of the radiation effect as well as sensitization leading to an increased efficacy without a corresponding increase in toxicity. On the basis of the above this study explores the potential use of the new physical treatment modality, TTFields, in combination with chemotherapeutic agents in cell cultures, an animal tumor model, as well as in patients with glioblastoma (GBM). As TTFields are not associated with systemic toxicity [1] the expectation is that their addition will result in an increase in efficacy alone.

Methods

Cell cultures

Cells were cultured and maintained as previously described [1,2]. In brief: Human breast cancer (MDA-MB-231) and human glioma (U-118) obtained from ATCC (USA) were cultured in DMEM + 10% FCS media in a 5% CO₂ incubator at 37°C. Drops consisting of 200 µl suspension of cells (100 × 10³ cells/ml) were placed at the centre of 35 mm Petri dishes, incubated for 2 hours to allow for cell attachment, then 1.5 ml of media were added and incubation was continued for an additional 22 h. Following this, the baseline cell count was estimated using the XTT colorimetric method (expressed as OD₀). The media in the Petri dishes was replaced by fresh media (3 ml), with or without a chemotherapeutic agent and incubated at a final temperature of 37° ± 0.5°C for 24 to 72 hours after which the cell number was re-estimated (OD_t). The relative number of viable cells at each time point following baseline was expressed as OD_t/OD₀ and treatment efficacy as the % change in proliferation relative to control:

$$(OD_t/OD_0)_{\text{experiment}} \cdot 100 / (OD_t/OD_0)_{\text{control}} \quad (1)$$

TTFields treatment of cultures

As previously described [1,2], two pairs of electrodes, insulated by a high dielectric constant ceramic, were positioned normal to each other at a distance of 20 mm in treatment and control dishes. In the former, the electrodes were connected to sinusoidal waveform generator that generated fields of optimal frequencies in the medium [1,2,9]: 150 kHz for breast cancer and 200 kHz for glioma, that changed direction by 90° every 250 ms. Field intensity was measured as described previously [2] and expressed as V/cm. For 72 h experiments the TTFields intensity of 1.75 V/cm was used. For 24 h experiments 0.65, 1.25 and 1.75 V/cm TTFields were used.

Four different sets of experiments were conducted in conjunction with each chemotherapeutic agent: untreated sham control, treatment with TTFields, treatment with the chemotherapeutic agents, and combined TTFields - Chemo treatment.

Assessment of combination index and dose reduction index

The Chou and Talalay [10] method for assessing the combined effect of multiple drugs was used for the drug - TTFields combinations. In order to assess whether the interactions between TTFields and each of the chemotherapeutic agents is synergistic, additive or antagonistic, combination indexes were calculated as follows; TTFields intensity replaced the concentration (dose) variable in the analyses. Dose-response curves were generated for TTFields and each drug to determine the median effect

points. Variable ratios of drug concentrations to TTFIELDS intensities were used to calculate the Combination Indexes (CI) as follows:

$$CI = (C_{Drug}(incombination), X\% effect / C_{Drug}(alone), X\% effect) + (I_{TTFIELDS}(incombination), X\% effect / I_{TTFIELDS}(alone), X\% effect) \quad (2)$$

Where: C are the drug concentrations and I the TTFIELDS intensities used to achieve a preset X% effect. Relationships of CI < 1 indicate more than additive - synergy, CI = 1 reflects additivity - summation and CI > 1 indicates less than additive or antagonism.

In order to assess whether TTFIELDS increase the sensitivity of tumor cells to various chemotherapeutic agents, the dose reduction index (DRI) of for each of these agents was calculated according to [11]. In short, the median-effect plots were for each chemotherapy-TTFIELDS combination, were constructed. The ratio of affected to unaffected number of cells (f_a/f_u) was plotted versus drug concentration on a log-log scale. The median effect point (D_m) was assessed by deriving the slope of the linear regression for each of the plots. The DRI for a 50% effect (DRI_m) was calculated as the ratio of D_m for drug alone and for combined drug-TTFIELDS:

$$DRI_m = D_m(drug\ alone) / D_m(combined\ treatment) \quad (3)$$

A DRI greater than 1 indicates an increase in sensitivity to the drug. The greater the DRI, the more significant the possible dose reduction.

In-vivo experiments

Combined TTFIELDS and Paclitaxel efficacy study in VX2 tumor bearing rabbits was conducted after approval by the NovoCure Internal Animal Care and Use Committee. All painful or anxiogenic procedures were performed under general anesthesia induced by intramuscular administration of 30 mg/kg of ketamine hydrochloride, 10 mg/kg xylazine hydrochloride and 1.5 mg/kg Acepromazine. The tumor tissue required for implantation was obtained from VX-2 tumor bearing carrier rabbits. The carrier rabbits had VX-2 tumors implanted intramuscularly in the thigh. When the tumor reached approximately 1 cm in diameter (about 3 weeks from implantation), the tumor was excised, minced in sterile saline and VX-2 tumor fragments obtained. Two fragments were injected using a large bore needle into the thigh, muscles of both legs in a recipient rabbit for tumor propagation. For experimental animals, after laparotomy, a fragment of tumor tissue (1 mm³) was implanted beneath the kidney capsule of the recipient rabbit.

The current experiment comprised 28 animals (7 in each of 4 groups). Fourteen days after tumor implantation the

initial tumor volume was assessed based on serial (2.2 mm interval) T1 weighted axial MRI images (1.5 Tesla, GE Genesis-Signa) obtained 3 minutes following IV injection of 3 ml of Gadolinium. Tumor volume was assessed from the area of the contrast enhancing lesion in each section. The animals were assigned randomly into 4 groups before treatment start:

1. TTFIELDS treated group: TTFIELDS were applied by using the NovoTTF-100A device (NovoCure LTD., Haifa, Israel). An optimal frequency of 150 kHz and intensity of 1-2 V/cm were used. TTFIELDS were switched sequentially between two perpendicular field directions.

2. Control group: sham electrode heated to mimic heat generated by the TTFIELDS treatment. (38-39.9°C)

3. Paclitaxel (Medixel Injection, Taro Pharmaceutical Industries LTD., Israel) treated group: 3 mg/animal diluted in 100 ml of normal saline were infused intravenously over a period of 30 minutes. Premedication was given subcutaneous 8 hours before and immediately prior to Paclitaxel administration (Dexamethasone (Dexaveto-0.2 veterinary, V.M.D n.v.s.a Belgium) 0.5 mg/animal; Pramine (Metoclopramide HCL, Rafa Laboratories LTD., Israel) 1 mg/animal; Diphenhydramine (10%, Medical M., Israel) 10 mg/animal).

4. Combined TTFIELDS and Paclitaxel treatment as above.

TTFIELDS were delivered to awake and behaving rabbits through four insulated electrode arrays placed circumferentially around the animal's abdomen, caudal to the ribcage. The electrode insulation consisted of a high dielectric constant (>10,000) ceramic (PMN-PT) allowing efficient energy transfer through the insulation into the animals body at the given frequencies. The electrodes were connected by a spiral cable to a swivel mechanism at the top of the cage, enabling the free movement. TTFIELDS were generated using the NovoTTF-100A system (NovoCure Ltd., Haifa, Israel). The animals were treated for 21 days continuously with MRI performed on days 14 and 21 for tumor volume assessment. The TTFIELDS intensity within the kidneys of the rabbits, using this electrode configuration, is between 1-3 V/cm (based on both finite element mesh simulations and direct measurements using an invasive probe - data not shown).

Pilot clinical trial

A single arm, pilot trial of the safety and efficacy of TTFIELDS treatment was performed in 20 patients with histologically proven glioblastoma multiforme (GBM) that met the inclusion/exclusion criteria specified in Supplemental Material Appendix A (briefly, KPS 70-100%, Age ≥ 18). The trial was performed according to a protocol

approved by the Na Homolce Institutional Review Board and the Czech Republic Ministry of Health. The patients were divided into two groups: The first group included 10 patients with recurrent GBM treated with TTFields alone following failure of maintenance Temozolomide [1]. The second group consisted of 10 newly diagnosed patients who were at least 4 weeks post radiation therapy, who received TTFields combined with maintenance Temozolomide. Prior to initiation of treatment, all patients underwent a baseline contrast MRI of the head, chest radiograph, ECG, ECG, complete blood & urine analyses, physical examination and neurological status. The patients were hospitalized for 1-3 days for observation and then released home where they received multiple 4-week courses of continuous NovoTTF-100A treatment until progression. The patients were seen once/month at an outpatient clinic where they underwent an examination similar to the initial one. TTFields were applied to the patients using the NovoTTF-100A device set to deliver 200 kHz, 0.7 V/cm (RMS) fields (at the center of the brain) in 2 perpendicular directions, 1 second in each direction sequentially. The TTFields were applied continuously using four insulated electrode arrays, each having a surface area of 22.5 cm², placed on opposing sides of the head with the tumor positioned directly between the electrode pairs [1]. As previously reported, to avoid electrolysis at the electrode surface and intracellular ion concentration changes that accompany long term current application, the electrodes were completely insulated by a ceramic having a very high dielectric constant (>10,000) that allowed the generation of the necessary electric fields [1,2]. Using this electrode configuration, the lowest TTFields intensity at the center of the brain was 0.7 V/cm (RMS). This intensity was calculated using finite element mesh simulations and verified by direct measurement in large animals and a human volunteer [1].

The outcome endpoints of the study included safety, overall survival (OS) and progression free survival (PFS). Assessment of tumor response was based on monthly MRIs according to the Macdonald criteria [12]. Median OS and PFS were determined using Kaplan Meier curves [13]. In the first group, PFS in NovoTTF-100A treated patients was compared to a matched group of concurrent control patients who received salvage chemotherapy at recurrence (n = 10). PFS in Temozolomide/NovoTTF-100A treated patients was compared to the PFS of a

matched group of concurrent control patients (n = 32) who received Temozolomide alone (according to the protocol described by Stupp et al. [14]). OS in both groups was compared to matched historical control data with the same Karnofsky performance score (>60) and age [14].

Results

Breast cancer cell cultures

Dose-response of culture exposure to TTFields, paclitaxel, doxorubicin and cyclophosphamide, alone and in combination
The relationship between TTFields intensity, at 150 kHz, and cell proliferation rate is given in Figure 1A. At the lowest field intensity of 0.63 V/cm there is no significant change in cell proliferation. For TTFields intensities of 1.25, 1.75 and 2.95 V/cm cell proliferation decreases (control = 100%) to: $90 \pm 3\%$, $74 \pm 4\%$ and $25 \pm 5\%$, respectively. The dose-response curves of cells exposed to paclitaxel, doxorubicin and cyclophosphamide, alone and in combination with 1.75 V/cm TTFields for 72 hours, are given in Figures 1B, C & D. For each drug alone there is a decrease in cell proliferation with increase in concentration. For cyclophosphamide and doxorubicin complete inhibition of proliferation is achieved at high drug concentrations. For paclitaxel, the inhibitory effect of the drug saturates at about 300 nM, near the 13% level, indicating that a fraction of the cells are insensitive to the agent. Combined treatment with TTFields and each of the chemotherapeutic agents caused a leftward shift of the dose response curves. This shift can be expressed as a decrease in the drug concentration leading to 50% inhibition of cell proliferation (IC₅₀ - Table 1).

Time course of the effects TTFields, paclitaxel, doxorubicin and cyclophosphamide

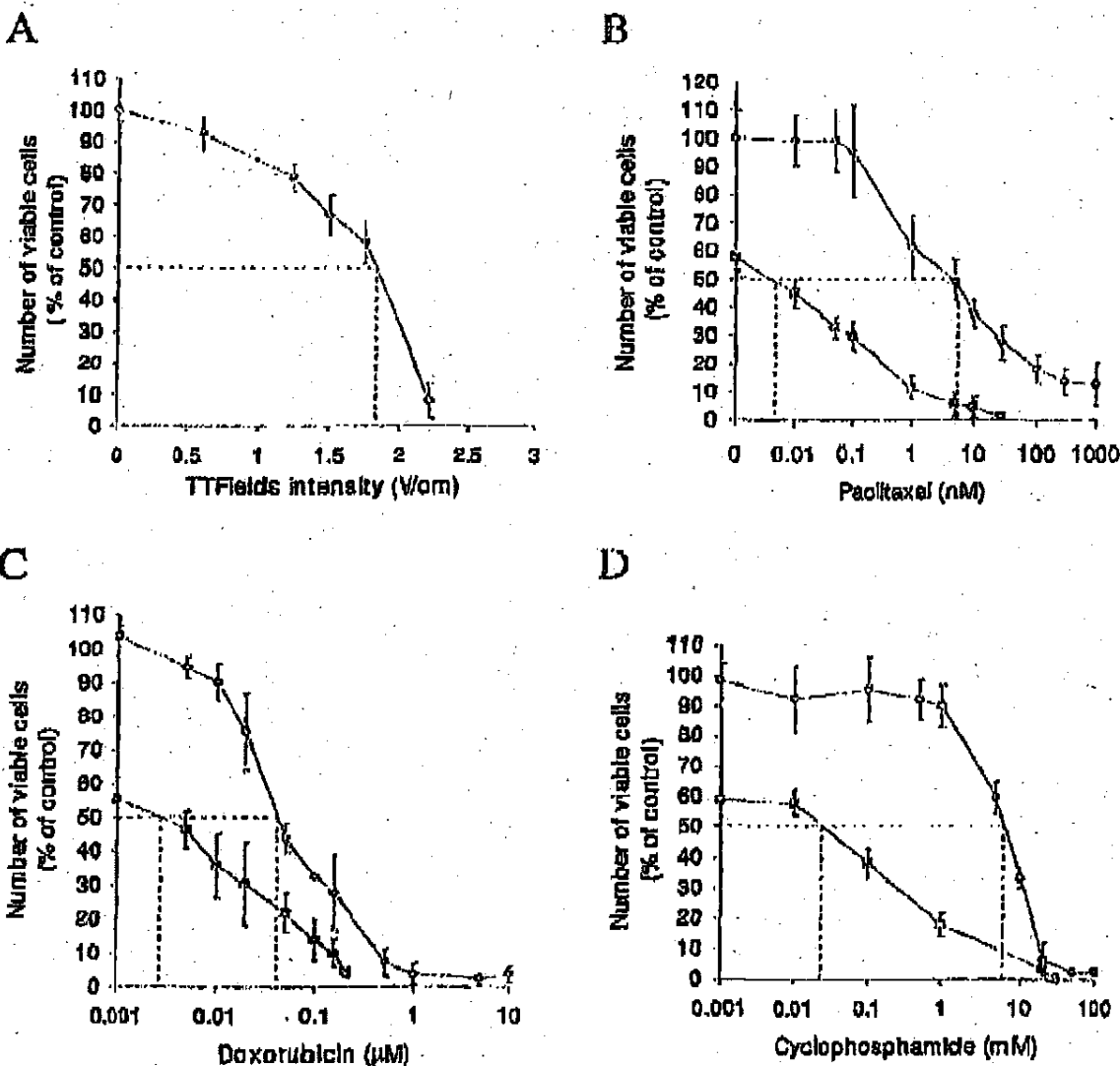
Figure 2 displays the time course of proliferation inhibition during a continuous 72 hour exposure to TTFields, paclitaxel, doxorubicin and cyclophosphamide alone and in combination with 1.75 V/cm TTFields. It is seen that in all cases the inhibition during combined exposure is greater than for the chemotherapeutic agent alone. The differences between the separate and combined effects increase with time.

Recovery from treatment

Figure 3 demonstrates that a 24 hour exposure to individual chemotherapeutic agents induces a reduction of approximately 25% in viable cell number compared to

Table 1: IC₅₀ for chemotherapeutic drugs alone and in combination with 1.75 V/cm TTFields after 72 hours of continuous treatment.

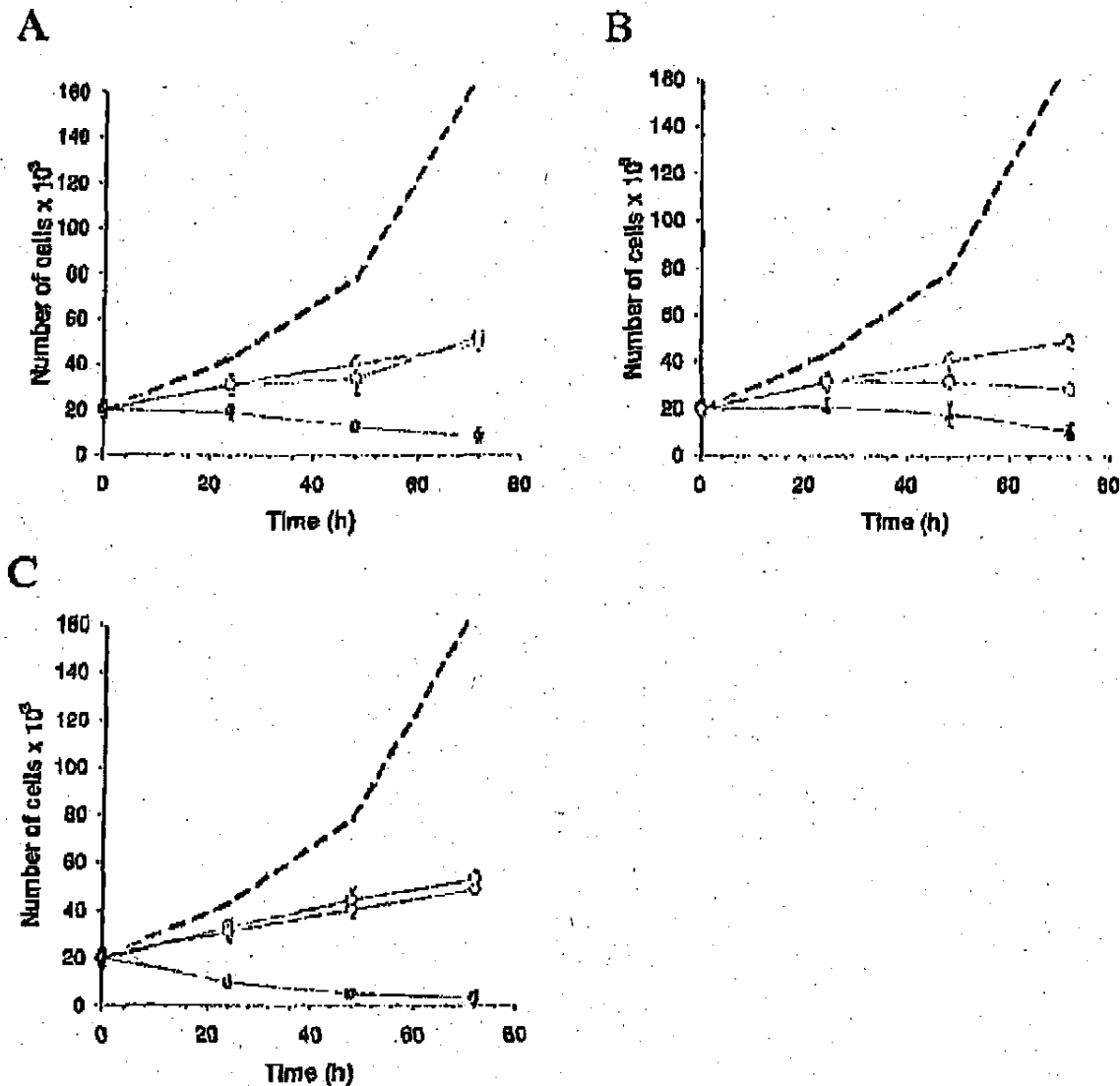
| Chemotherapy | IC ₅₀ (drug alone) | IC ₅₀ (drug-TTFields combination) |
|------------------|-------------------------------|----------------------------------------------|
| Paclitaxel | 5.00 nM | 0.005 nM |
| Doxorubicin | 0.04 μM | 0.002 μM |
| Cyclophosphamide | 0.60 mM | 0.044 mM |

**Figure 1**

Effect of 72 hour continuous application of TTF fields and chemotherapeutic agents, separately and in combination on the cell proliferation of ER-negative MDA-MB-231 cells (presented as percent viable cells compared to control). (A) Percent viable cells vs. TTF fields intensity. Effect of different concentrations of paclitaxel (B), doxorubicin (C) and cyclophosphamide (D), alone and in combination with TTF fields of 1.75 V/cm. In B, C and D Filled Circles – represent drug alone; Filled Squares – drug in combination with TTF fields. Each point represents mean values \pm SEM of 18 to 36 replicate measurements. Dotted lines demarcate the IC₅₀ values for each curve.

controls. The proliferation rate (slope of the graph) recovers almost completely during the following 48 hours, except for doxorubicin, where recovery is slower and

delayed by about 24 hours. In contrast, addition of TTF fields to any one of these chemotherapeutic agents results in irreversible and complete inhibition of cell pro-

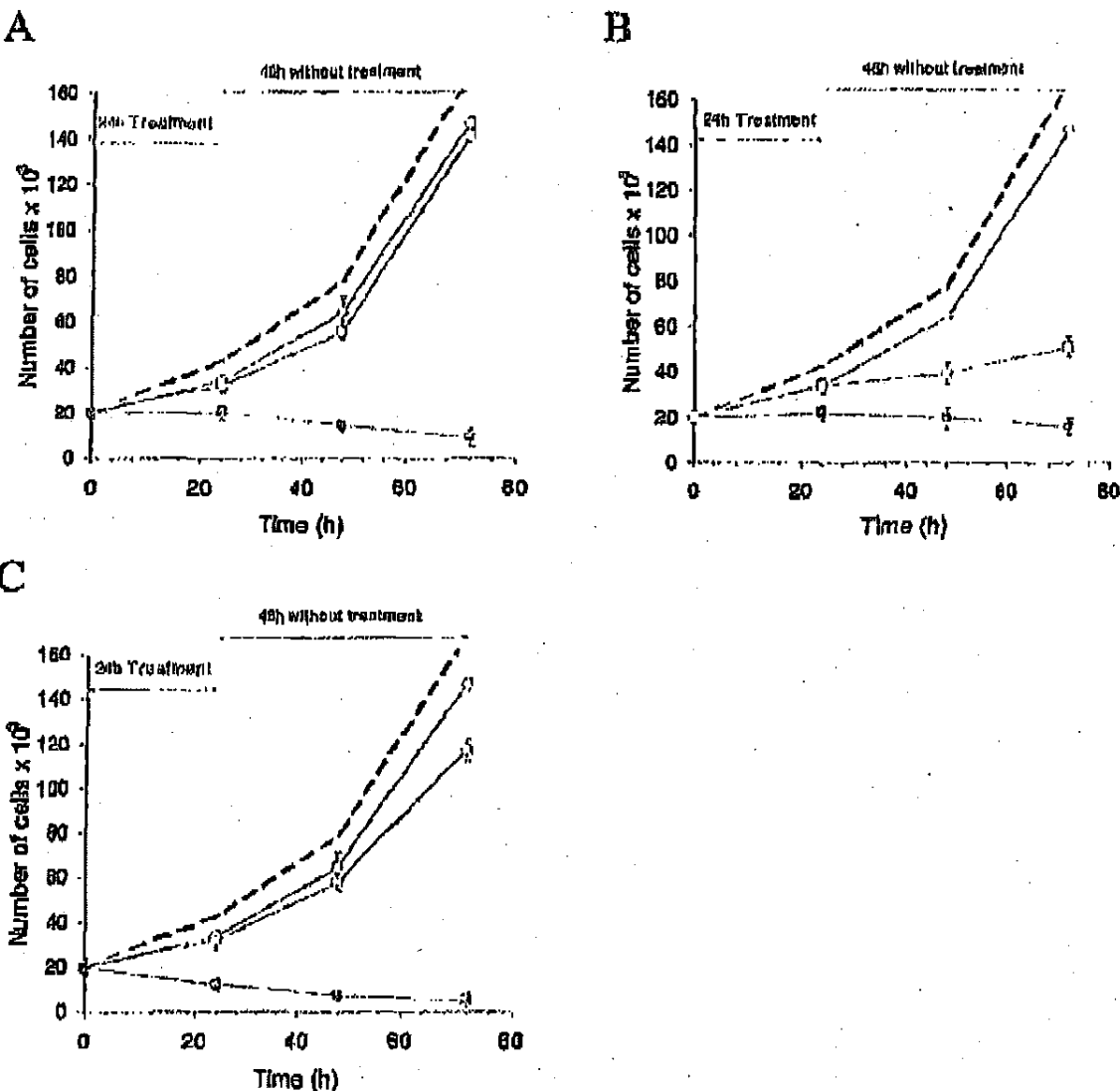
**Figure 2**

Time courses of the effects of 72 hour exposure of MDA cells to Paclitaxel (A), Doxorubicin (B) and Cyclophosphamide (C) alone and in combination with 1.75 V/cm TTFields. Each graph shows the number of viable cells in culture over time in control cells (interrupted lines), drug alone (open squares), TTFields alone (open circles) and drug-TTFields combination (closed squares). Data are presented as mean \pm SEM. Each experimental condition included 18–36 samples.

liferation rate manifested as a decrease in the number of cells in culture. For Cyclophosphamide there is an almost complete loss of viable cells after 72 hours of combined treatment.

Glioma cell cultures

Combined effect of DTIC and TTFields in human glioma cell cultures
In order to assess the combination between Temozolomide and TTFields in glioma cells, DTIC and TTFields

**Figure 3**

Time course of recovery from 24 hour exposure to Paclitaxel (A), Doxorubicin (B) and Cyclophosphamide (C) alone and in combination with 1.75 V/cm TTFields. Each graph shows the number of viable cells in culture over time in control cells (interrupted lines), drug alone (open squares), TTFields alone (open circles) and drug-TTFields combination (closed squares). Data are presented as mean \pm SEM. Each experimental condition included 18-36 samples.

were applied alone and in combination to U-118 cells in culture. Both DTIC and Temozolomide act through a common degradation product (MTIC). Thus light activated DTIC was used for these experiments as described

previously [15,16]. Figure 4 compares the DTIC dose-response curve, with that obtained with DTIC - TTFields combination. As we have shown in breast cancer cultures, the addition of TTFields to a chemotherapeutic agent

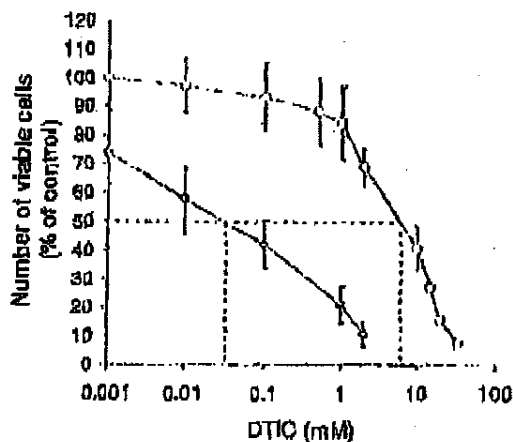


Figure 4
Effect of light activated DTIC and TTFields (1.75 V/cm) on cell proliferation of U-118 glioma cells, presented as percent of viable cells compared to control. Open Circles - 72 hours of DTIC treatment alone. Filled Circles - 72 h of Combined DTIC - TTFields treatment.

causes a leftward shift in the dose-response curve in glioma cells as well. The IC_{50} for DTIC alone in Figure 4 is 6.4 mM, whereas the IC_{50} for combined DTIC-TTFields is two orders of magnitude lower (0.023 mM).

Analysis of combination efficacy and sensitivity in-vitro Combination indexes

The mode of interaction between TTFields and chemotherapeutic agents (synergism, additivity or antagonism) can be analyzed using Combination Indexes (CI) as described by [10,17]. In order to calculate the CIs for TTFields-Chemotherapeutic agents, the extent of inhibition of cell growth was assessed after 24 hours of treatment with Paclitaxel, Doxorubicin and Cyclophosphamide alone or in combination with different intensities of TTFields (0.625-1.75 V/cm; see Materials and Methods). Table 2 demonstrates that for breast cancer cells the CI for Doxorubicin is very close to 1, indicating additivity [10,11]. In contrast, for TTFields with Paclitaxel and Cyclophosphamide the CIs are <1 indicating additivity with a tendency towards synergism.

Dose reduction indexes

In order to assess the extent of possible chemotherapeutic dose reduction when applied in combination with TTFields, dose reduction indexes (DRI) for each drug-TTFields combination were calculated based on the meth-

Table 2: Calculated Combination Indexes for human breast cancer (MDA-MB-231) cells treated with paclitaxel, doxorubicin or cyclophosphamide in combination with TTFields.

| TTFields Intensity (V/cm) | Combination index | | |
|---------------------------|-------------------|-------------|------------------|
| | MDA-MB-231 cells | | |
| | Paclitaxel | Doxorubicin | Cyclophosphamide |
| | CI_{10} | CI_{10} | CI_{50} |
| 0.625 | - | - | 0.74 |
| 1.25 | 0.97 | 0.99 | 0.84 |
| 1.75 | 0.86 | 0.98 | 0.95 |

odology described by [11]. The DRIs for TTFields-drug interaction after 72 hours of combined treatment was 1316 for paclitaxel, 23 for doxorubicin, 152 for cyclophosphamide and 175 for DTIC (in U-118 glioma cells). Thus a significantly reduced dose (1-3 orders of magnitude lower drug concentration) may be used in combination with TTFields to achieve the same level of efficacy.

Effect of combined paclitaxel and TTFields on VX2 tumors in rabbits

Prior to testing the combined efficacy of paclitaxel and TTFields on VX2 tumors implanted within the kidneys of rabbits, the dose-response of paclitaxel in this animal tumor model was determined. A dose of Paclitaxel leading consistently to a 15-20% inhibition in tumor growth (5 mg/rabbit) was chosen for subsequent combination experiments with TTFields.

As seen in Figure 5, untreated tumors increased in volume by a factor of 70 from baseline. Paclitaxel treated tumors grew by a factor of 58 from baseline. TTFields treated tumors grew by a factor of 94 from baseline and tumors treated by TTFields-Paclitaxel combination grew by a factor of 22 from baseline. Thus the TTFields-Paclitaxel combination treatment inhibited tumor growth by 69% compared to the growth of control tumors, while Paclitaxel alone inhibited tumor growth by 15% compared to the growth of control tumors, and TTFields alone by 53% compared to the growth of control tumors. Thus, additivity was seen between TTFields and Paclitaxel at the intensity and concentration used. Differences between curves were statistically significant ($p < 0.01$; ANOVA).

Pilot clinical trial in GBM patients

Twenty patients with histological diagnosis of GBM were treated continuously for an average of 1 year (range 2.5-24 months). Ten recurrent GBM patients were treated with TTFields alone as salvage therapy. Ten newly diagnosed

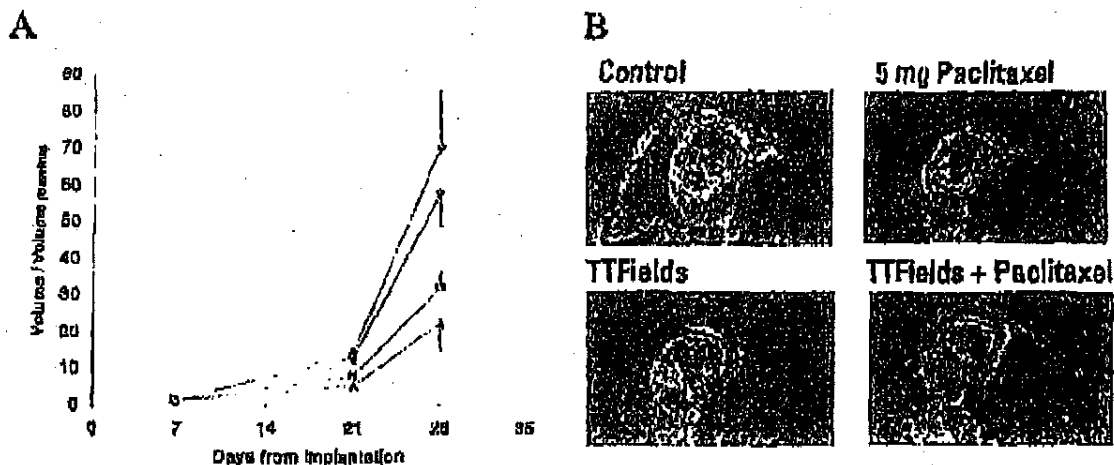


Figure 5

Effect of combined Paclitaxel/TTFIELDS on VX2 tumors in Rabbits. A VX-2 Kidney tumor volumes were normalized to pre-treatment tumor volume (day 7) and are presented over time for: control (diamonds), 5 mg Paclitaxel (circles), TTFIELDS (squares) and combined TTFIELDS-Paclitaxel (triangles). The effect of combined TTFIELDS and Paclitaxel is equal to the sum of the effects of either treatment alone at both time points measured during the study (2 and 3 weeks from treatment start; $n = 23$; bars are standard errors of means). B Exemplary MRIs of the maximal contrast enhancing tumor area (demarcated by orange borders) in the kidneys of rabbits in each of the experimental groups (sham control, Paclitaxel 5 mg, TTFIELDS 2 V/cm, combined Paclitaxel and TTFIELDS).

GBM patients, that had undergone surgery and thereafter received radiation therapy with adjuvant Temozolomide, were treated with the combination of TTFIELDS in parallel to maintenance Temozolomide [14]. In both groups of patients no device related serious adverse effects were observed. The only device related toxicity reported was a dermatitis which appeared most often (18 of 20 patients) during the second month of treatment. The severity of the dermatitis decreased upon use of topical corticosteroids and periodic electrode relocation. The dermatitis continued for the duration of treatment and resolved completely within days to weeks from treatment termination.

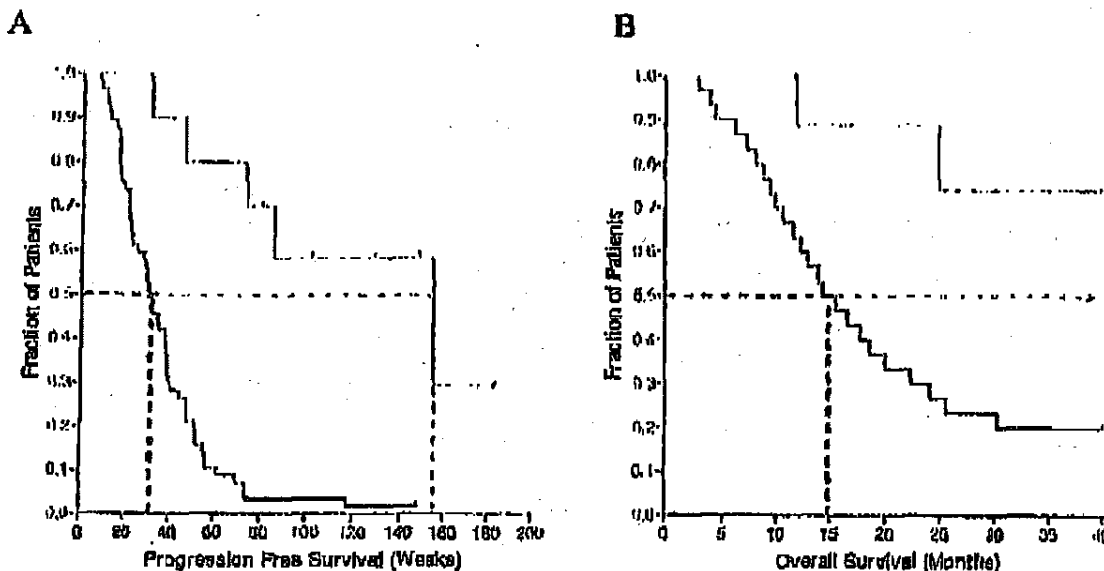
In the second group, no increase in Temozolomide related adverse events was seen due to the combination with TTFIELDS (see Table 3).

As reported previously [1], both progression free survival (PFS) and overall survival (OS) in the recurrent GBM salvage therapy group were at least double that of concurrent and historical controls, respectively. The efficacy of the TTFIELDS-Temozolomide combination in the second group of patients was assessed using Kaplan Meier curves [13] of PFS and OS. The Kaplan Meier curves for the PFS of these patients, treated by combined TTFIELDS - Temozolomide are shown in Figure 6A. The median PFS of the

combination treated patients is 155 weeks versus 31 weeks for concurrent controls treated with maintenance Temozolomide alone. Note that 5 of 10 patients are currently progression free. Figure 6B compares the OS of the patients that received the combination treatment (dotted line) with a matched historical control (KPS>60, Median age 54) (thick line [14]). It is seen that for the TTFIELDS - Temozolomide combination treated patients, the Median OS > 39 months versus about 14.7 months for matched historical control patients who received maintenance Temozolomide alone. It should be noted that at the time

Table 3: Toxicities by grade and causality in this newly diagnosed GBM patients treated with combined TTFIELDS-Temozolomide.

| | Grade | | Causality assessment |
|------------------|-------|--------|----------------------|
| | I-II | III-IV | |
| Elevated LFTs | 0/10 | 0/10 | Anti Epileptic Drugs |
| Hyperglycemia | 4/10 | 0/10 | Oral Steroids |
| Anemia | 6/10 | 0/10 | Temozolomide |
| Thrombocytopenia | 2/10 | 0/10 | Temozolomide |
| Leucopenia | 3/10 | 0/10 | Temozolomide |
| Headache | 2/10 | 0/10 | Underlying disease |
| Seizures | 1/10 | 0/10 | Underlying disease |
| Dermatitis | 10/10 | 0/10 | Novo TTF-100A |

**Figure 6**

Kaplan Meier curves for **A** - progression free survival (PFS) and **B** - overall survival (OS) of newly diagnosed GBM patients receiving either combined TTFIELDS - Temozolomide treatment or Temozolomide treatment alone. Red line - patients receiving combined TTFIELDS - Temozolomide treatment (n = 10). Black line - concurrent/historical control patients that received Temozolomide treatment alone. **A** - The difference between the PFS curves is highly significant - Log-Rank Test ($P = 0.0002$), Hazard Ratio 3.32 (95%CI 1.9-5.9). **B** - The difference between the OS curves is highly significant - (Log-Rank Test; $P = 0.0018$). Dashed lines mark the median values for each curve.

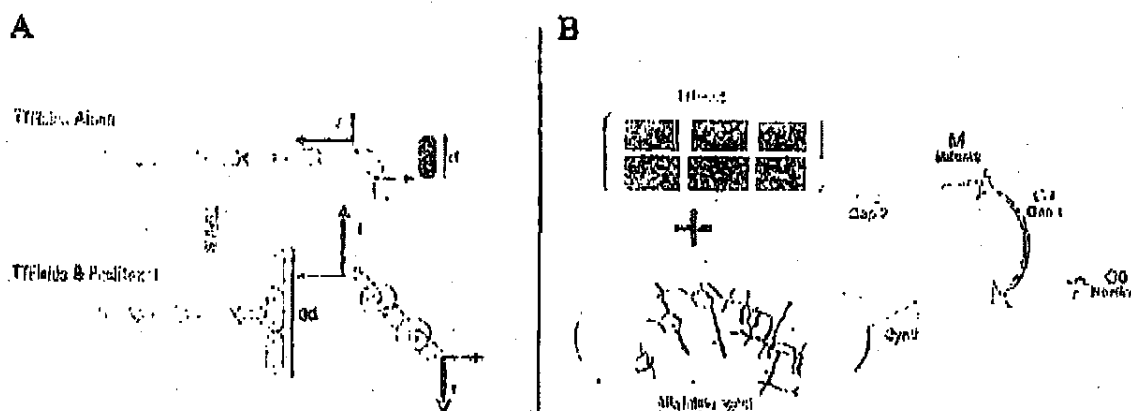
of this report 8 of 10 patients, receiving the TTFIELDS-Temozolomide combination treatment, are alive.

Discussion

Cancer treatment with drug combinations was introduced in order to improve therapeutic indexes through dose reduction of each drug and increase treatment efficacy. In this study the exposure of cancer cells to combined chemotherapy and TTFIELDS was studied in cell cultures, an animal tumor model and in a pilot clinical trial in recurrent and newly diagnosed GBM patients. The results of this study support the possibility that TTFIELDS may be used, not only as an effective stand alone anti-proliferation agent (as shown previously in [1]), but also as an effective adjuvant that enhances chemotherapy efficacy without an increase in toxicity. In addition to this increase in efficacy, these results raise the possibility of dose reduction of chemotherapy when used in combination with TTFIELDS. This is of utmost importance since, at tolerable doses the efficacy of available cancer therapeutic agents is often far from optimum while being associated with a high degree of toxicity.

With regards to the mechanisms involved, one may assume that tumor cells are sensitized to TTFIELDS by chemotherapy, much like another well established physical therapy - ionizing radiation [8,18,19]. In the specific case of Paclitaxel, one of the most commonly used treatments for late-stage human breast cancer [20], the combined effect may be attributed to their similar site of action - the spindle microtubules [1,2,21]. Taxanes act by stabilizing the link between individual tubulin dimers [21]. As illustrated schematically in Figure 7A taxanes increase the length of tubulin filaments within the cell. One of the mechanisms of action of TTFIELDS is the misalignment of mitotic spindle filaments as a result of TTFIELDS forces on tubulin chains [2]. The increase in filament length due to taxanes, increases the dipole moment of these macromolecules, leading to an increase in the TTFIELDS induced forces and thus to a higher sensitivity of the cell to TTFIELDS (see Figure 7A).

Doxorubicin that has a broad spectrum of activity both in experimental tumor models and in human malignancy, affects both DNA and RNA synthesis [22]. Cyclophosphamide (an alkylating agent) inhibits DNA replication by

**Figure 7**

Mechanisms of potentiation of chemotherapeutic efficacy by TTFields. A Tubulin chains are elongated by Paclitaxel, leading to an increase in the average dipole moment of free tubulin chains (d = length of an individual tubulin dimer; F = force between the microtubule chain and the dimer; F = force acting on the tubulin dimers by TTFields; Arrow length is proportional to the intensity of these forces). The forces TTFields exert on these larger dipoles, F , are enhanced leading to an increase in the disruption of the mitotic spindle by TTFields. B TTFields act as an M-phase inhibitor, while alkylating agents act at the G and S phases of the cell cycle. This separation between cell cycle phases affected explains the additivity seen experimentally.

interfering with the separation of the double stranded DNA essential for transcription [29]. As illustrated in Figure 7B, since TTFields act at a completely different stage (M phase) of the cell cycle from both these agents, additivity between chemotherapy and TTFields can be expected.

Since the data for newly diagnosed GBM patients, which points to well over a 300% increase in PFS and OS, was obtained only with combination treatment, one cannot directly separate the TTFields effects from the chemotherapeutic effect. However, if we assume that the TTFields therapeutic efficacy for newly diagnosed patients is similar to recurrent GBM, i.e. the median of OS is increased by 270% [1] while the published Temozolomide data indicates an increase of about 20% in OS compared to ionizing radiation treatment alone [14], the results presented in Figure 6 point towards additivity between TTFields and Temozolomide. It is important to note that this significant increase in efficacy was obtained without any increase in device or drug related toxicity (see table 3).

An additional important finding is that both 24 h and 72 h combination treatments in-vitro result in severe irreversible cellular damage in contrast to chemotherapy alone. This result strengthens the assumption that combination therapy with TTFields may be much more effective than treatment by individual agents.

Conclusion

The results of the present study support the notion that TTFields may be used clinically not only as an anti-proliferation agent as shown before [1], but also as effective sensitizers of currently used chemotherapeutic agents. Such sensitization was not shown to be associated with any additional systemic toxicity. Moreover, as demonstrated by the high DRIs calculated in this study, chemo/TTFields combinations are expected to provide the same or even greater therapeutic efficacy with much lower drug concentrations thus lowering further the overall toxicity.

Competing interests

BK, RSS, AI, DM, ZG, ES and YW are employees of NovoCure Ltd.

YP has a minority holding in NovoCure Ltd.

VD, FT, JV and DG have no competing interests.

Authors' contributions

BK - planned the pre-clinical and clinical experiments, supervised their execution, analyzed results and wrote parts of the manuscript. RSS and ET - Performed the in-vitro experiment and assisted in the in-vivo experiments. DM, ZG and AI - Performed the in-vivo experiments. DG - Performed the MRI imaging for the in-vivo experiments. YW - Planned the medical devices and treatment parameters.

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ers for all experiments. VD, FT and JV - performed the clinical trial in GBM patients (clinical investigators). YD - invented the concept of TTFIELDS, helped interpret all results and wrote the majority of the manuscript.

Appendix

Appendix A - Eligibility criteria for the pilot GBM trial

Inclusion criteria:

Histologically proven diagnosis of GBM.

Age over 18 years.

Karnofsky scale ≥ 70 .

Participants of child bearing age had to be receiving efficient contraception.

Willing and able to sign an informed consent prior to participation in the study.

Exclusion criteria:

Patients actively participating in another clinical trial

Patients who received any anti-tumor therapy in the four weeks prior to trial initiation (steroids are permitted; however, the dose must be stable or decreasing during the trial).

Patients suspected of suffering from radiation necrosis (according to a PET scan).

Pregnancy

Patients with one of the following co-morbidities:

Patients with an implanted pacemaker or documented arrhythmias.

Significant renal, hepatic or hematologic disease.

Significant additional neurological disorder

Seizure disorder unrelated to the patient's tumor

Pre-existing dementia

Progressive degenerative neurological disorder

Meningitis or encephalitis

Hydrocephalus associated with increased intracranial pressure (ICP)

Acknowledgements

We wish to thank Mr. Michael Portanski and Mrs. Orly Azrad for providing technical support and study coordination for the clinical study. Both MF and OA are employees of NovoCure Ltd. EK, RS, AI, DM, ZG, ES and YV are employees of NovoCure Ltd. VD, FT, and JV performed the clinical trial which was sponsored by NovoCure Ltd.

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Pre-publication history

The pre-publication history for this paper can be accessed here:

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1. Background
2. TTFields's mechanism of action
3. Preclinical studies with TTFields
4. Clinical studies with TTFields
5. Summary
6. Expert opinion

Tumor treating fields: concept, evidence and future

Miklos Pless[†] & Uri Weinberg[†]Medical Oncology, Department of Internal Medicine and Tumor Center, Kantonsspital Winterthur, Winterthur, Switzerland

Introduction: Local control is fundamental, both for the curative as well as the palliative treatment of cancer. Tumor treating fields (TTFields) are low intensity (1 - 2 V/cm), intermediate frequency (100 - 200 kHz) alternating electric fields administered using insulated electrodes placed on the skin surrounding the region of a malignant tumor. TTFields were shown to destroy cells within the process of mitosis via apoptosis, thereby inhibiting tumor growth. TTFields have no effect on non-dividing cells.

Areas covered: This article reviews *in vitro* and *in vivo* preclinical studies, demonstrating the activity of TTFields both as a monotherapy as well as in combination with several cytotoxic agents. Furthermore, it summarizes the clinical experience with TTFields, mainly in two indications: one in recurrent glioblastoma multiforme: In a large prospective randomized Phase III trial TTFields was compared with best standard care (including chemotherapy). TTFields significantly improved median overall survival (OS) compared with standard therapy (7.8 vs 5.1 months) for the patients treated per protocol. Importantly, quality of life was also better in the TTFields group. The second indication was a Phase II study in second-line non-small cell lung cancer, where TTFields was administered concomitantly with pemetrexed. This combination resulted in an excellent median OS of 12.8 months. Interestingly, the progression-free survival (PFS) within the area of the TTFields was 28, however, outside the TTFields the PFS was only 22 weeks.

Expert opinion: The proof of concept of TTFields has been well demonstrated in the preclinical setting, and the clinical data seem promising in various tumor types. The side effects of TTFields were minimal and in general consisted of skin reaction to the electrodes. There are a number of ways in which TTFields could be further evaluated, for example, in combination with chemotherapy, as a maintenance treatment, or as a salvage therapy if radiotherapy or surgery is not possible. While more clinical data are clearly needed, TTFields is an emerging and promising novel treatment concept.

Keywords: cancer, electric fields, glioblastoma, non-small cell lung cancer, TTFields

Expert Opin. Investig. Drugs [Early Online]

1. Background

Alternating electric fields have been used since many years for the diagnosis, research and treatment of various medical conditions. Such electric fields have different properties, depending on their frequency and intensity (Table 1). Very low frequencies (lower than 1 kHz) are used to excite the membrane of muscles and nerves, thereby leading to membrane depolarization and finally to action potentials (AP). Higher frequency alternating electric fields penetrate cells better, but the overall effect of hyper-depolarization on the cell membrane balances in a way that the integral stimulation does not yield an action potential. However, at frequencies higher than 10 MHz, the electrophysiological properties of the eukaryotic

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Tumor treating fields: concept, evidence and future

Article highlights.

- Tumor treating fields (TTFields) are low intensity (1 – 2 V/cm), intermediate frequency (100 – 200 kHz) alternating electric fields, which can induce apoptosis.
- TTFields are able to inhibit tumor growth in various cell lines and animal models.
- The combination of TTFields with several cytotoxic agents resulted in a supra-additive tumor growth inhibition *in vitro* and *in vivo*.
- Two clinical trials, a Phase III trial in glioblastoma multiforme (GBM) and a Phase II study in non-small cell lung cancer (NSCLC) have shown antitumor activity of TTFields.
- Toxicity was low; it consisted mainly of skin reactions at the site of the electrodes.

This box summarizes key points contained in the article.

membrane lead to dielectric polarization that eventually heats the tissue (4,5). Intermediate-frequency alternating electric fields, at frequencies between 10 kHz and 1 MHz, neither cause net depolarization nor significant dielectric losses, therefore, cannot stimulate nerves/muscles, but also cannot seriously heat tissues at low enough intensities. It was thought that such electric fields have no meaningful biological effect on cells (4,6-9). Nevertheless, it was recently found that such fields, named tumor treating fields (TTFields), have an anti-mitotic activity and may lead to the death of dividing cells. The fields were found to have these properties already at a very low intensity (< 2 V/cm) and at intermediate frequency of 100 – 300 kHz.

2. TTFields's mechanism of action

Each cell contains numerous electrically charged molecules, such as proteins and DNA. Under an alternating electric field, these molecules will oscillate according to the changing direction of the field and its density (Figure 1). If the field is uniform, the forces acting intermittently to opposite directions will cause a movement parallel to the direction of the field. When the frequency of the field is high enough, such as in the case of TTFields, this molecular movement will reduce. In the case of dipoles, where there is an electric split between the positive and negative poles of a molecule, it will align with the direction of the electric field and remain at the same place. All charged molecules, including dipoles, will move toward the higher field density in a non-uniform alternating electric field. Within a non-dividing cell, the field is mostly uniform and the net force on charges and dipoles will, therefore, yield minimal movement. Non-uniform electric fields, on the other hand, force polar molecules to move toward higher field intensity, in a process called dielectrophoresis (10,11). Such fields are characteristic of dividing cell when a narrow furrow connects the two forming daughter cells.

2.1 Arrest of mitotic spindle formation

Mitotic spindle is the organelle that separates the cell's chromosomes to each of the daughter cells during mitosis. The arms that hold to the chromosomes consist of small polar molecules called tubulins, which polymerize to form a 'chain' of subunits that will reach the genetic material at the center of the cell. As noted before, the field is uniform within the non-dividing cells, but the tubulin subunits will tend to align according to the direction of the field. Finite element simulations showed that the electrical forces acting on the subunits prevent them from attaining the orientation required for efficient polymerization, therefore, mitosis becomes arrested for an abnormally long time (12). This happens since subunits far enough from the growing microtubule will be subjected to an electric force strong enough to prevent further polymerization. When this process takes place, cells could either complete mitosis or disintegrate.

2.2 Mitotic furrow destruction

Not all cells seem to be affected by means of disruption of mitotic spindle formation. The membranes of cells that completed metaphase will start dividing into two daughter cells, pulling the daughter chromosomes to each of the cells' poles. During the last step in mitosis, that is, cytokinesis, a cleavage furrow is eventually formed, which completes the process of cell separation. This narrow membranous link results in an hourglass-shaped non-uniform electric field, unlike non-dividing cells, in which the electric field is uniform. During cytokinesis, the densest electric field is found in the narrow center. This focusing of the field directs all electric charges and dipoles to the furrow due to the unidirectional character of the electric force (dielectrophoretic force) under this condition. Finite element simulations have shown that polarized molecules and organelles within the cell will be affected by forces high enough to move toward the furrow so as to disrupt the internal cell structure and cause the cell destruction seen under TTFields therapy (12).

3. Preclinical studies with TTFields

A number of preclinical trials have shown the efficacy of TTFields in the inhibition of cancer cell proliferation and their destruction *in vitro* (12,13). Many cell lines were cultured and tested under TTFields, among others melanoma, glioma, lung, prostate and breast cancer. TTFields was applied continuously for 24 – 72 h. In all cases, proliferation was significantly inhibited, compared with control cultures and to non-replicating cultures (baby hamster kidney (BHK) cells) treated with TTFields. For some of the cell lines, a specific optimal frequency that demonstrated maximal inhibitory effect was found, possibly reflecting different cell size and shape (Table 2) (13). Under time-lapse microscopy, cancer cells demonstrated significantly prolonged mitosis and even cell destruction on the formation of the cleavage furrow. Immunohistochemistry studies of cell cultures treated with TTFields showed many abnormal

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Table 1. Alternating electric fields used in medicine

| Frequency | Biological activity | Application |
|---------------|------------------------------|---------------------------------------------------------|
| < 1 kHz | Membrane depolarization | Defibrillators, ECT, bone growth, fracture healing, ICD |
| 100 - 300 kHz | Mitotic arrest and apoptosis | TTFields |
| 1 - > 10 MHz | Dielectric polarization | Diathermy, radio frequency tumor ablation |

ECT, electroconvulsive therapy; ICD, implantable cardioverter-defibrillator; TTFields, tumor treating fields.

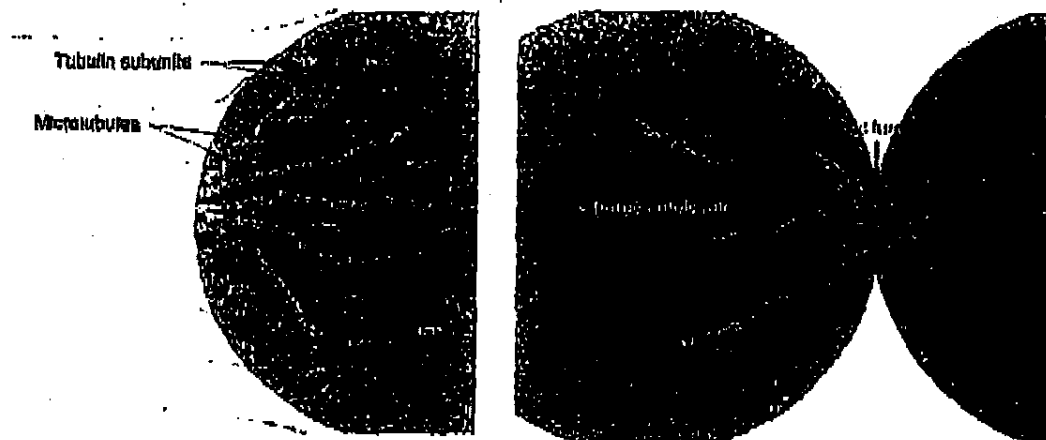


Figure 1. Antimitotic effects of tumor treating fields (TTFields). At the beginning of mitosis, the electric field is uniform within the cell, causing tubulin subunits to align with the direction of the field and inhibiting their polymerization to form a normal microtubule spindle. In a non-uniform electric field formed during cytokinesis, charges and dipoles move toward the high field density at the mitotic furrow, disrupting mitosis and disintegrating the daughter cells.

mitotic figures that could be related to the interference of TTFields with the mitotic spindle formation. These figures resemble the prosecution of cancer cells treated with agents that interfere with mitotic spindle formation, such as paclitaxel. Further experiments showed that the efficacy of TTFields in combination with different chemotherapies is additive and could be synergistic (14).

Interestingly, TTFields caused cultured cells to orient in the direction of the electric field (15). This could be explained by the fact that the electric forces are maximal when the axis of division is aligned with the external field. This also implies that the angle of the cell affects its vulnerability to TTFields during mitosis.

TTFields was also shown to inhibit tumor growth in several mouse, rat and rabbit animal models (12,13). Implanted cell lines were used to test the most effective frequency and intensity for this *in vivo* treatment. Postmortem analysis of the treated animals showed a significant tumor size reduction in the case of TTFields-treated animals, compared with control animals. No difference of the local temperature in the vicinity of the tumor was found between the two groups. *In vivo* experiments showed that it is possible to deliver the field to the target region using

insulated non-invasive electrodes. While there was no statistically significant inhibition of tumor growth when a unidirectional TTFields was delivered this way, two- and three-directional fields led to a statistically significant growth inhibition (15). *In vivo* tumor models have shown dose-time optimization in tumor inhibition when using the effective specific frequency for each cell type. No abnormality in vital signs, electrocardiograms (ECG), complete blood counts (CBC), chemistry and coagulation panels was found during the follow-up period of animals treated with TTFields, and no treatment-related pathologies were found postmortem.

In a metastatic melanoma mouse model and metastatic kidney cancer rabbit model, TTFields was shown to reduce the extent of metastatic spread, possibly due to metastasis growth inhibition, migration capability impairment and primary tumor local control (15).

4. Clinical studies with TTFields

Prior to applying TTFields to human patients, feasibility was tested using finite element method (FEM) simulations and measurements within the brain of a volunteer undergoing brain

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Tumor treating fields: concept, evidence and future

Table 2. Optimal TTFields frequency for tested cell lines

| Cell line | Optimal frequency (kHz) |
|-----------------------------|-------------------------|
| B16F1 (mouse melanoma) | 120 |
| AA8 (Chinese hamster ovary) | 150 |
| VX-2 (rabbit kidney) | 150 |
| MCF-7 (human breast) | 150 |
| MDA-MB-231 (human breast) | 150 |
| F-98 (rat glioma) | 200 |
| U-87 (Human glioma) | 200 |
| U-118 (Human glioma) | 200 |

TTFields, tumor treating fields.

surgery. It was found that TTFields can be effectively applied to the occiput using surface electrodes. TTFields was first tested on 10 recurrent malignant glioblastoma multiforme (GBM) patients. No concomitant chemotherapy was used during the clinical trial, and TTFields was the only antitumor therapy. TTFields was delivered via a portable, light-weight (~ 3 kg) device carried by the patient (NovoTTFields-100A, NovoCure Ltd, Haifa, Israel), connected to two pairs of insulated electrodes that were applied to the patients' skin. The device continuously (18 h/day on average) delivered two perpendicular 1–2 V/cm, 200 kHz alternating electric fields (Figure 2). Patients had a highly significant increase in the median time to disease progression (26.1 weeks) and progression-free survival (PFS) at 6 months (50%) compared with historical controls, with a median overall survival (OS) of more than 62 weeks [13]. In addition, no treatment-related serious adverse event was detected in a total of 280 treatment weeks. The only treatment-related adverse event was mild-to-moderate contact dermatitis beneath the electrode gel, which was easily managed using topical treatments.

These preliminary findings led to a Phase III clinical trial of TTFields compared with best standard of care chemotherapy in 237 patients with recurrent GBM [16,17]. Patients in this study were previously treated with an unlimited number of surgeries/chemotherapy cycles. They were randomized to either a TTFields arm, given as a monotherapy without additional antitumor treatments, or to the best standard chemotherapy (BSCh) arm, which was at the treating physician's discretion. TTFields was administered continuously and patients' compliance was excellent, with a median duration of 20 h/day. Patient characteristics were balanced in both groups, with median age of 54 years and median Karnofsky performance status (KPS) of 80%. Mean treatment duration was 4.4 months in the TTFields group versus 2.3 months in the BSCh group. In the group of 185 patients who were treated per protocol, a statistically significant survival benefit was seen for the TTFields group (median OS 7.8 vs 6.1 months for TTFields and BSCh, respectively). Moreover, patients with better prognostic baseline characteristics (KPS 80% or higher, age 60 or lower) demonstrated an even higher survival benefit when treated with TTFields (median OS 8.8 vs 6.6 months; $n = 110$). These results show that TTFields

as a monotherapy are at least as effective as the best available chemotherapy or supportive care in this poor prognosis disease. It is noteworthy that quality of life (QOL) was equivalent or superior in patients treated with TTFields compared with BSCh. This clinical trial also showed that the only TTFields-related adverse events were mild-to-moderate contact dermatitis beneath the electrodes in a minority of patients. The incidence of toxicities was significantly higher in the BSCh arm.

TTFields was also explored in a Phase III single arm study in combination with pembrexed for advanced (stage IIIB/IV) non-small cell lung cancer (NSCLC) as a second-line treatment, after failure of standard first-line chemotherapy [18]. Electrodes were applied to the chest and upper abdomen and the device (NovoTTFields-100 L, NovoCure Ltd) generated 150 kHz TTFields, in accordance with the preclinical findings relating to lung cancer cell lines. Forty-one patients were treated, including 7 (17.1%) with squamous cell carcinoma and 30 (72.9%) with stage IV disease. The device was well tolerated and the average daily use was 11.2 h. No TTFields-related serious adverse event was reported for a cumulative time of over 720 weeks. Median PFS was 22 weeks and in-field PFS (i.e., PFS within the area of the TTFields; the study's primary end point) in the lungs and liver was 28 weeks. This is an important finding because it can be assumed that in the same patient the higher tumor control within the TTFields area was a specific effect of TTFields. Median OS was 13.8 months and 1-year survival was 57% (Figure 3). Six patients (14.6%) had a radiological partial remission (PR) and 16 patients had stable disease (SD) (39%). These results are very promising and compare extremely well with matched historical controls treated with pembrexed alone in second-line treatment [19].

Special attention was given to potential adverse events using TTFields: in the glioblastoma trial careful neurological examination and documentation was required once a month. In the lung cancer trial, BCGs were mandated at the beginning of the trial, during the treatment if adverse effects occurred and at the end. Finally, skin reactions were monitored at every visit and documented according to the National Cancer Institute (NCI)-Common Toxicity Criteria (CTC) (version 3.0) in all studies. All other adverse events were monitored routinely at every visit according to the CTC criteria. In all studies involving TTFields the only side effect, which occurred more frequently was grade 1–2 skin toxicity. In the glioblastoma trial there was a direct control group, in the lung cancer trial we compared the side effects with the large Phase III study by Hanna *et al.*, in which pembrexed was given as a second-line treatment [19].

5. Summary

TTFields was shown to inhibit proliferation and to cause cell destruction of many cancer cells *in vitro* and *in vivo*. In addition, TTFields significantly improved human patients' prognosis in recurrent GBM and probably also in NSCLC. At the time this review was submitted, there were no serious adverse events found related to TTFields.

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and pain were excellent, compared with historical data for pemetrexed alone (18).

The good safety profile along with the significant clinical efficacy and QOL advantages make TTFields an attractive treatment in GBM, and perhaps in many other malignancies.

5. Expert opinion

TTFields is a novel and promising concept for treating solid tumors. *In vitro* and *in vivo* experiments have repeatedly shown a significant inhibitory effect on cancer cell proliferation upon application of TTFields. We already know that at least two physical mechanisms are involved: the first is interference with the mitotic spindle formation as a result of electric forces preventing the normal polymerization of the tubulin subunits. The second mechanism results from the non-uniformity of the electric field in the context of cytokinesis, and the movement of molecules in the direction of the mitotic furrow as a result of the unidirectional force generated by TTFields.

There are also some data indicating that combining chemotherapeutic cancer treatments with TTFields may increase efficacy and sensitivity to chemotherapy (14). Several tumor types are sensitized to radiation after adding different chemotherapies, even at low doses (24,25). Could some tumors similarly be more susceptible to TTFields treatment if treated concomitantly with certain cytotoxic agents? This is a plausible idea, since TTFields acts on specific organelles (e.g., the mitotic spindle), which are also the target of some of the anticancer drugs. Taxanes act through stabilizing the link between tubulin dimers in the spindle microtubules. It could be that the abnormal increase in microtubule length caused by this class of agents, which leads to the formation of a larger dipole moment, results in an increase in the efficacy of TTFields (14). This possible synergism could be used to achieve a better response, but alternatively also as a way to decrease chemotherapy toxicity in patients who cannot tolerate the toxicity of full-dose chemotherapy. The fact that TTFields itself was not toxic and in combination with pemetrexed did not increase the known side effects of the latter in this clinical trial mentioned above, makes combination therapies an attractive therapeutic option.

Preclinical experiments showed the frequency-dependent effect of TTFields, with different frequencies showing a maximal inhibitory effect in certain cancer cell types (13). In the future, it will be interesting to see how this characteristic could be exploited in order to maximize the effect, by adjusting the frequency on an individual tumor basis, using cytological/pathological specimens for the analysis. Such adjustments could be possible for tumors of the same entity but in different patients, and maybe even at different stages in the course of the same disease.

Other fields of interest that will probably be investigated in the future include the pathway in which cell death occurs following exposure to TTFields. Unpublished findings show that apoptosis is the process that leads to cancer cell death



Figure 2. The tumor treating fields (TTFields) generating portable device (NovoTTFields-100A).

On the contrary, the treatment was toxicity-free for treated patients, except for mild-to-moderate contact dermatitis underneath the electrodes. Importantly, there was no cardiac or neurological abnormalities as a result of TTFields treatment. The use of non-invasive surface electrodes prevented flow of ionic currents (26,27) or cell death (22) as a result of direct currents, and thus decreased skin damage and enabled continuous treatment.

TTFields can actively inhibit different cell types, including multi-drug-resistant (MDR) ovarian and breast cancer cell lines that overexpress ABC (ATP-binding cassette) transporters (28). It may not only be useful in the treatment of locally advanced tumors, but also in the prevention and treatment of metastatic disease. TTFields has the potential to inhibit the migration of metastases from a primary tumor. It can inhibit the growth of metastases in the lungs once they have been seeded in the target organ, through the presence of the fields in the lungs themselves.

In the first Phase III study published to date (16,17), TTFields had minimal toxicity and patients' compliance was excellent, over an extended period of time. The application of TTFields resulted in an improved median OS, higher response rate and longer time to treatment failure compared with best standard chemotherapies and also led to an improvement in many QOL parameters. A large-scale Phase III clinical trial in newly diagnosed GBM is currently being conducted.

In the first clinical trial for NSCLC patients, TTFields was well tolerated in a second-line setting. It was safe and efficacy

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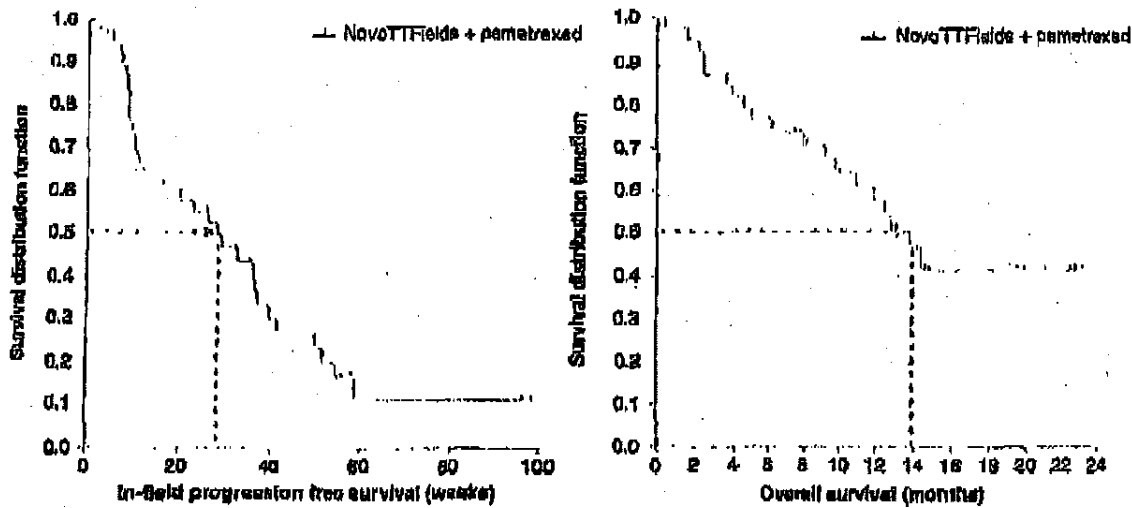


Figure 2. Phase II trial using tumor treating fields (TTFields) in combination with pemetrexed in non-small cell lung cancer as a second-line therapy. Median in-field progression-free survival (PFS) was 28 weeks. Median overall survival (OS) was 13.3 months; $n = 41$.

Adapted from poster presentation ESMO 2010 [6].

under TTFields. Finding the specific pathway through which apoptosis is carried out will provide a better understanding of the basic mechanism and will pave the way for other combinations or treatment optimization. The immune system plays an important role in the pathogenesis of cancer [27]. TTFields has the potential to beneficially affect the microenvironment of the tumor: it could act directly on recruited immune cells, alternatively, it could change the interaction between these cells and the tumor following changes to the tumor cell structure, vasculature, etc. Preliminary data show that there is a change in the presence of immune cells that interplay with cancer cells, following TTFields treatment [19].

Both the Phase III (for recurrent GBM patients) and the Phase II (for advanced NSCLC) trials have given some important insights on using TTFields [16–18]. The high compliance demonstrates that it is feasible to administer TTFields continuously using a light-weight portable device, in spite of the necessity to be attached to the device. Since most patients enrolled in the trials were somewhat hindered by their malignant disease, they generally adjusted to TTFields quite quickly and well. In the NSCLC trial, the majority of patients used TTFields overnight and was free at daytime. It can be assumed that other cancer patients will tolerate TTFields as well. It will be interesting to see how other chemotherapies administered concomitantly to TTFields will affect the course of these patients. A Phase III trial (NCT00916409) for newly diagnosed GBM patients treated with a combination of temozolomide and TTFields is currently ongoing.

As a physical treatment modality, TTFields has the potential to be active in other solid tumors as well. In a pilot study,

TTFields therapy was very well tolerated and safe for four patients bearing skin lesions from breast and melanoma tumors. These tumors showed transient inhibition in the growth rate during a 2- to 4-week treatment and the findings warrant further investigations [28]. While systemic chemotherapy usually has significant toxicities, biologically targeted therapies often affect only a subset of tumors carrying specific mutations or proteins. Glioblastoma and NSCLC, like many other tumors, harbor many different genotypes [29–31] and it has been difficult to show a major impact of chemotherapy or even targeted agents in these tumor types, at least for the majority of patients. TTFields acts independently of the expression of cell surface receptors or other tumor biomarkers. There are no alternative escape mechanisms, thus cancer cells are unlikely to be or to become resistant to TTFields.

There are several ways of further developing TTFields clinically. TTFields is a regional treatment: it could be employed in situations where radiotherapy is not possible anymore, for example, after a full course of radiation to the brain. Another option would be to test it in situations in which prophylactic radiotherapy is used for example, prophylactic cranial irradiation (PCI) small cell lung cancer, hopefully circumventing the late toxicity of PCI. Lastly, it can of course be tested together with radiotherapy. Even though TTFields is a regional treatment, it still managed to decrease the likelihood of metastases formation in animal experiments [13], the most common cause of death in cancer. It could be that TTFields was able to prevent malignant cell evasion from the primary tumor in the lung cancer treated population, thereby leading to decreased formation of micrometastases [18].

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In summary, TTFields could be considered as a potential effective treatment for patients suffering from different cancer types. The non-toxic characteristics and promising clinical outcomes in several clinical trials conducted to date should encourage investigators to further evaluate TTFields, either as a monotherapy or in combination with other treatments.

Declaration of Interest

M Pless declares no conflict of interest. U Weinberg works for Novocure Ltd. as Medical Director. Novocure has supported experiments described in this review and was the sponsor for the clinical trials. The paper was not supported by a commercial company.

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Accepted for publication 10/10/2018

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JULY 2, 2013

RE: [REDACTED]
Medicare Number [REDACTED]

Dear [REDACTED]

This letter is about our decision in your appeal to ANTHEM BLUE CROSS ILLINOIS AND EQUALITY INS COMPANY (Anthem). You asked Anthem to pre-approve the NovoTTF 100-A system (electrical field therapy) in [REDACTED].

Our decision

We agree with you. This means that we will tell Anthem to pre-approve the NovoTTF 100-A system. To learn more about how we made our decision, read the following pages of this letter.

What you have to do

We sent Anthem a copy of this letter, so they know they have to pre-approve the NovoTTF 100-A system.

Make sure the NovoTTF 100-A system is obtained through Anthem. Otherwise, Anthem may not pay for it.

Anthem has to pre-approve the item or service or make plans to pre-approve the item or service within 72 hours. If Anthem does not do so within 72 hours, call the Chicago CMS Regional Office at 312-333-7130

Chicago CMS Regional Office

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FORM 1041-VOL INVOICE 01/01/2010 11:45:00 AM FIVE 2/000 1041-VOL INVOICE

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How we made our decision

1. We read all the papers in the file.
2. We checked McGowan's notes.
3. We checked the contract with Anthem.
4. We sent the file to a MAXIMUS Federal Services Doctor Consultant.

To make our decision we read all the papers in the file very carefully. We used the Medicare rules. We looked to see if Anthem correctly followed Medicare rules and regulations.

Medicare rules say that the health plan must give the member a subscriber agreement. It is a contract between the health plan and the member. It is usually called the "Evidence of Coverage" (EOC) or "Member Agreement." We read this contract carefully to see what Anthem is supposed to cover.

We sent the case to a MAXIMUS Federal Services Doctor Consultant. This doctor works for us, not the health plan. We asked this doctor to review all of the medical records in the file.

Medicare rules

The rules say that health plans must pay for a medical service or item if regular Medicare would pay for it. In this case, You can find this rule at 42 CFR §422.101.

The rules say that medically necessary services are those that are reasonable and necessary for the diagnosis or treatment of an illness or injury. Medically necessary services include services to improve the functioning of a malformed body member. You can find this rule at Social Security Act § 1862 (a)(1)(A).

If you want to read these Medicare rules, you can go to this web site www.medicareappeal.com.

The health plan contract

The health plan contract says that Anthem covers items and services in accordance with Medicare rules.

Doctor review

Our MAXIMUS Federal Services Doctor Consultant looked at the file for this case. This doctor says that the NovoTTF-100A system is medically necessary for [REDACTED]. Our doctor found that the patient presented in October 2012 with headaches, confusion and left hemiparesis. A MRI scan revealed a right fronto-temporal mass that was resected by December 2012. The pathology showed this tumor was a glioblastoma multiforme, WHO grade IV. She got temozolomide and concurrent radiation therapy but the tumor progressed. She had more surgery in March 2013 after which the NovoTTF device was recommended. In 2011, the FDA approved the NovoTTF-100A device to deliver alternating electrical fields to treat recurrent GBM. The device has FDA approval and is appropriate to use in this patient who has exhausted standard chemotherapy options.

Explanation of decision

We decided that Amgen has to pre-approve the NovoTTF 100-A system (electrical field therapy).

1. *Chlorophyll a* and *Chlorophyll b* contents were determined by spectrophotometry using the method of Lichtenthaler and Whaley (1987).

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You asked Anthem to pre-approve the NovoTTF 100-A system. You say that this device is the only promising option for the patient at this time. Due to her orphan disease status, limited treatment options and favorable outcome and higher quality of life afforded with this treatment, you are requesting reconsideration of the denial. Anthem denied your request. Anthem says that the level of evidence is 2B (equivocal) in the current NCCN guidelines which is not sufficient to warrant medical necessity.

Anthem must follow Medicare rules. Medicare rules say that if there are no specific coverage rules for an item or service, then that item or service will be covered when it is medically necessary.

Our MAXIMUS Doctor Consultant says that the NovoTTF 100-A system is medically necessary for [REDACTED]. We looked at this doctor's review, the file and Medicare rules. Based on this information, we decided that Medicare rules for coverage of the NovoTTF 100-A system have been met. Therefore, we decided that Anthem has to pre-approve the NovoTTF 100-A system (electrical field therapy) for [REDACTED].

If Anthem does not agree with our decision, they can ask us to open a case again. We only open a case again if we believe there was a mistake or if there is new information to review. The health plan has to show us the mistake and/or send us the new information. This does not happen often. If we decide to open the case again, we will send you a letter.

PAM/1A



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MedTech

Brain tumor treatment device gets early trial halt for efficacy as a combo with chemo

by Stacy Lawrence | Nov 18, 2014 7:10am

The only FDA-approved, wearable cancer treatment device may expand its reach. A Phase III trial of Optune (NovoTTF-100A System) from Novocure was halted early due to statistically significant efficacy for the device in combination with chemotherapy to treat newly diagnosed glioblastoma patients.

This is an expansion upon its original indication approved by the FDA in 2011 for use as a monotherapy for recurrent glioblastoma after surgical and radiation options have been exhausted.

Founded in 2000, the startup has spent about \$250 million in pursuit of a tumor treatment device. Despite this massive infusion of cash—or perhaps because of it—Novocure remains a private company. It has at least three big, strategic corporate investors: Medtronic (\$MDT), Pfizer Venture Investments and Johnson & Johnson Development Corporation. In addition, WFD Ventures and Index Ventures back the somewhat controversial company. Device companies have a checkered history when it comes to efficacy in cancer treatment.



Optune in action—Courtesy of Novocure

The idea is to create tumor-treating electric fields that are delivered locally to the body via transducer arrays that are worn directly on the scalp. Patients must commit to wearing the obtrusive device at least 18 hours daily. The electric fields are designed to disrupt the process of cell division in the tumor, which divide at an accelerated rate compared with normal tissue. The company says the frequency is tuned to target only tumor cells, which are a certain size.

The new data from the EF-14 trial show that newly diagnosed glioblastoma patients treated with the device in combination with chemotherapeutic agent temozolomide have a statistically significant improvement in progression-free survival and in overall survival as compared with temozolomide alone. Specifically, the device and the chemo provided a median PFS of 7.1 months versus 4 months for temozolomide alone, while the combination offered 19.6 months median OS versus 16.6 months for temozolomide only.

After the first two years of the study, 43% of the patients in the device/temozolomide arm remained alive, while only 29% of the patients in the temozolomide were living. The trial was halted for efficacy, in order to offer the treatment to the remaining chemo-only group. The Independent Data Monitoring Committee conducted this prespecified interim analysis on the first 315 patients, which represented about half of the targeted trial population.



"These results are spectacular," Dr. Roger Stupp, director of the University Hospital Cancer Center at the University of Zurich and EF-14 principal investigator, said in a statement. "A new standard of care for patients suffering from glioblastoma is born."

Glioblastoma is the most common form of primary cancer in the brain, with about 10,000 patients diagnosed annually in the U.S. In addition to glioblastoma, Novocure is also in pilot testing for treatment of ovarian, pancreatic and non-small cell lung cancer as well as brain metastases. Its system was recently renamed Optune.

Novocure CEO Asaf Danziger

Novocure CEO Asaf Danziger added that the startup is "working closely with FDA" to make the device available to newly diagnosed glioblastoma patients "as soon as possible."

- here is the release on the data

- and here is a *New York Times* story that offers a poignant patient perspective (sub. req.)

Bad Blood: The book that reads like a late-night biotech horror movie | FierceBiotech

IMAGE REQUEST

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IMAGE UNDER:

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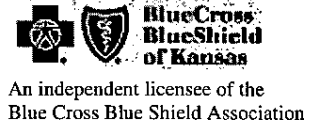
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JIMMO..... ☐

SPECIAL SCAN REQUESTS:

DATE NEEDED BY: _____ RETURN TO: _____



Title: Tumor Treating Fields Therapy

Professional

Original Effective Date: August 1, 2018

Revision Date(s): August 1, 2018

Current Effective Date: August 1, 2018

Institutional

Original Effective Date: August 1, 2018

Revision Date(s): August 1, 2018

Current Effective Date: August 1, 2018

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| Populations | Interventions | Comparators | Outcomes |
|---------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| Individuals: • With newly diagnosed glioblastoma multiforme on maintenance therapy after initial treatment | Interventions of interest are: • Tumor treating fields therapy as an adjunct to standard maintenance therapy | Comparators of interest are: • Standard maintenance therapy alone | Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity |
| Individuals: • With progressive or recurrent glioblastoma multiforme | Interventions of interest are: • Tumor treating fields therapy as an adjunct or alternative to medical therapy | Comparators of interest are: • Standard medical therapy | Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity |

DESCRIPTION

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

OBJECTIVE

The objective of this policy is to determine whether the use of tumor treating fields therapy improves the net health outcome for patients with solid tumors including glioblastoma multiforme.

BACKGROUND**Glioblastoma Multiforme**

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.¹ GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (eg, bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors.¹ The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to 1 year, and the 5-year survival rate was around 5%.²

Clinical Context and Therapy Purpose

The purpose of alternating electrical field therapy, more commonly known as tumor treating fields (TTF) therapy, is to provide a treatment option that is better than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

Treatment of Newly Diagnosed GBM

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these 2 therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles. Response and overall survival rates with temozolomide are higher in patients who have O⁶-methylguanine-DNA methyltransferase (*MGMT*) gene promoter methylation.

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice (see the Supplemental Information section).³ For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur essentially all patients.

Treatment of Recurrent GBM

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivascular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (eg, lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at 6 months is less than 20%.⁴ There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

The questions addressed in this evidence review are:

- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

Interventions

TTF therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields.⁴⁻⁶ TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. TTF therapy is proposed to inhibit tumor growth by 2 mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase.^{5,6} Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune (formerly NovoTTF-100A System) is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

Comparators

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

The following practices are currently being used to make decisions about recurrent GBM: medical therapy.

TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds 3 to 5 months.⁴

Outcomes

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

Timing

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.

Setting

The setting is outpatient care by an oncologist or neuro-oncologist.

REGULATORY STATUS

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process.⁷ The FDA-approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, FDA approved Novocure's request for a product name change from NovoTTF-110A System to Optune®.⁸

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.⁹ The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

FDA product code: NZK.

POLICY

- A. Tumor treating fields therapy to treat glioblastoma multiforme is considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:
1. Adult patients ≥ 18 years of age
 2. Supratentorial tumor
 3. Karnofsky Performance Status score $\geq 70\%$
 4. Patient understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the Food and Drug Administration label (see Policy Guidelines).
- B. Tumor treating fields therapy is considered **experimental / investigational** in all other conditions, including but not limited to, the following situations:
1. As an adjunct to standard medical therapy (eg, bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
 2. As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
 3. For brain metastases
 4. For cancer in areas other than the brain.

Policy Guidelines

1. Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth $> 25\%$ compared with the smallest tumor area measured in the patient during the trial or appearance of 1 or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).
2. The Food and Drug Administration label includes the following notices:
 - a. Patients should use Optune for at least 18 hours a day to get the best response to treatment
 - b. Patients should finish at least 4 full weeks of therapy to get the best response to treatment. Stopping treatment before 4 weeks lowers the chances of a response to treatment.

RATIONALE

The literature update was performed through April 5, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

For this review, 3 indications are evaluated: (1) tumor treating fields (TTF) as an adjunct to maintenance chemotherapy in newly diagnosed patients following initial treatment with surgery, radiotherapy and chemotherapy and (2) TTF as an adjunct or (3) alternative to medical therapy (eg, bevacizumab, chemotherapy) in progressive or recurrent glioblastoma multiforme (GBM).

Study Selection

The PICOTS was used to select relevant studies.

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Within each category of study design, studies with larger sample size studies and longer duration were sought.

TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM Randomized Controlled Trials

Stupp et al (2017) published results of the EF-14 multicenter, open-label phase 3 RCT that evaluated maintenance therapy with TTF for newly diagnosed GBM.¹⁰ The trial included 695 patients from 83 sites who had supratentorial GBM and had completed standard treatment consisting of biopsy or surgical resection followed by radiotherapy and chemotherapy (see Table 1). A Karnofsky Performance Status (KPS) score of 70 or higher was an additional inclusion criterion to ensure independence in activities of daily living, and patients with rapidly progressing GBM following radiochemotherapy were excluded from the trial. Patients were randomized in a 2:1 fashion to TTF plus maintenance temozolomide or maintenance temozolomide alone.

All patients were seen monthly for follow-up. Quality of life (QOL) was assessed every 3 months, and magnetic resonance imaging (MRI) was performed every 2 months until tumor progression. Tumor progression on MRI was adjudicated by a central review committee blinded to treatment group. The primary outcome was progression-free survival (PFS), and the secondary outcome was overall survival (OS). The analysis was by intention-to-treat, including 26 patients from the control arm who crossed over to TTF following the planned interim analysis.

In 2014, an independent data and safety monitoring board concluded from the planned interim analysis that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended trial termination. The Food and Drug Administration approved the trial termination, and the trial was closed to recruitment with 695 of the planned 700 participants randomized. Control arm participants were allowed to cross over to the experimental treatment at this time. The interim analysis, which the Food and Drug Administration considered for the 2015 expanded approval of Optune, was published by Stupp et al (2015).¹¹ At the time of the interim analysis, data were available for 210 patients randomized to TTF plus temozolomide and 105 patients to temozolomide alone. Follow-up of the remainder of the 695 enrolled patients continued after enrollment was closed.

Table 1. Key Randomized Controlled Trial Characteristics for Newly Diagnosed Glioblastoma

| Study; Trial | Countries | Sites | Dates | Participants | Interventions | |
|------------------------------------------|---------------------------------|-------|-----------|-----------------------------------------------------------------------------------|----------------------------------------------------|----------------------------------------------------------------------|
| | | | | | Active | Comparator |
| Stupp et al (2017) ¹⁰ ; EF-14 | U.S., E.U., South Korea, Israel | 83 | 2009-2016 | 695 newly diagnosed with GBM and treated by radiochemotherapy KPS score ≥ 70 | TTF > 18 h/d plus maintenance temozolomide (n=466) | Maintenance temozolomide alone (5 d every 28 d for 6 cycles) (n=229) |

GBM: glioblastoma multiforme; h/d; hours per day; KPS: Karnofsky Performance Status; TTF: tumor treatment fields.

Results of the final analysis of the EF-14 trial were similar to the interim analysis and are shown in Table 2. Both PFS and OS improved with the addition of TTF therapy to standard maintenance chemotherapy (ie, temozolomide). PFS increased by 2.7 mo ($p < 0.001$) and OS increased by 4.9 mo ($p < 0.001$) in the TTF group. The time to a decrease in mental function was 2.5 months longer with TTF therapy ($p < 0.01$).

There was a similar percentage of dropouts at the final analysis—with 49 (11%) patients in the TTF group and 27 (12%) patients in the temozolomide alone group. More treatment cycles with temozolomide were administered in the TTF group (median, 6 for TTF group vs 5 for controls), a finding that is consistent with the longer PFS. Rates of adverse events were similar between the groups, including rates of seizures. In secondary analysis of patients who had not progressed, there was no reduction in health-related quality of life with TTF compared with temozolomide alone aside from "itchy skin".¹² Interpretation of this result is limited by the low percentage of patients who completed the health-related quality of life assessments at follow-up (65.8% of the 655 patients alive at 3 months and 41.7% of the 473 patients alive at 12 months). A mixed-model analysis, which accounts for missing data, confirmed the results of the mean change from baseline analysis.

Table 2. Key Randomized Controlled Trial Results for Newly Diagnosed Glioblastoma

| Study | Final N (%) | Median PFS (95% CI), mo | Median OS (95% CI), mo | Systemic Adverse Events, n (%) | Seizures, n (%) | Time to 6-Point Decline in MMSE Score (95% CI), mo |
|----------------------------------|-------------|-------------------------|------------------------|--------------------------------|-----------------|----------------------------------------------------|
| Stupp et al (2017) ¹⁰ | | | | | | |
| TTF + temozolomide | 417 (89) | 6.7 (6.1 to 8.1) | 20.9 (19.3 to 22.7) | 218 (48) | 26 (6) | 16.7 (14.7 to 19.0) |
| Temozolomide alone | 202 (88) | 4.0 (3.8 to 4.4) | 16.0 (14.0 to 18.4) | 94 (44) | 13 (6) | 14.2 (12.7 to 17.0) |
| HR (95% CI) | | 0.63 (0.52 to 0.76) | 0.63 (0.53 to 0.76) | | | 0.79 (0.66 to 0.95) |
| P value | | < 0.001 | < 0.001 | 0.58 | | 0.01 |

CI: confidence interval; HR: hazard ratio; MMSE: Mini-Mental State Examination; OS: overall survival; PFS: progression-free survival; TTF: tumor treatment fields.

Tables 3 and 4 display notable gaps identified in this trial, the major limitation is the lack of patient blinding to treatment assignment. However, PFS was assessed by investigators who were blinded to treatment and placebo effects on OS were expected to be minimal. Investigators considered it practically unfeasible (due to the heat and current of the TTF therapy) and ethically unacceptable to submit the control patients to repeated shaving of the head and continuous wear of a sham device over many months.

Table 3. Relevance Gaps

| Study; Trial | Population ^a | Intervention ^b | Comparator ^c | Outcomes ^d | Follow-Up ^e |
|------------------------------------------|-------------------------|---------------------------|----------------------------------------------------------------------------------|-----------------------|------------------------|
| Stupp et al (2017) ¹⁰ ; EF-14 | | | 3. Possible differences in post-progression treatment affecting overall survival | | |

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 4. Study Design and Conduct Gaps

| Study; Trial | Allocation ^a | Blinding ^b | Selective Reporting ^c | Data Completeness ^d | Power ^e | Statistical ^f |
|------------------------------------------|-------------------------|------------------------------------------------------------|----------------------------------|--------------------------------|--------------------|--------------------------|
| Stupp et al (2017) ¹⁰ ; EF-14 | | 1. No sham control and not blinded to treatment assignment | | | | |

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

* Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

† Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM

The final analysis of the EF-14 trial, which included 695 patients from 83 sites, found a statistically and clinically significant increase of 2.7 months in PFS and an increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. There was no sham control, and patients were not blinded to treatment assignment, but PFS was assessed by blinded evaluators, and placebo effects on the objective measure of OS were likely to be minimal. There was no evidence of a negative impact of TTF therapy on health-related quality of life, except for itchy skin from the transducers.

TTF Therapy as an Adjunct or Alternative to Medical Therapy for Progressive or Recurrent GBM

Randomized Controlled Trials

The 2011 Food and Drug Administration approval of the NovoTTF-100A System (now called Optune) was based on a phase 3 multinational RCT (EF-11), results of which were published by Stupp et al (2012).⁴ This trial compared TTF therapy alone with physician's choice medical therapy in 237 adults who had relapsed or progressive glioblastoma (see Table 5). Patients had failed conventional treatment with radiotherapy, chemotherapy, and/or surgery, and more than 80% of participants had failed 2 or more prior chemotherapy regimens. In this trial, the term chemotherapy also applied to targeted agents such as bevacizumab. Patient characteristics and performance of additional post-recurrence debulking surgery were similar in the 2 groups.

Table 5. Summary of Key Randomized Controlled Trial Characteristics for Progressive or Recurrent Glioblastoma

| Study; Trial | Countries | Sites | Dates | Participants | Interventions | |
|-----------------------------------------|--------------------|-------|-----------|-------------------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------------------------------------------------|
| | | | | | Active | Comparator |
| Stupp et al (2012) ⁴ ; EF-11 | U.S., E.U., Israel | 28 | 1987-2013 | 237 adults with relapsed or progressive supratentorial glioblastoma KPS score $\geq 70\%$ | 120 patients treated with TTF alone, 93 (78%) completed 1 cycle | 117 patients treated with physician's choice of medical therapy ^a |

EU: European Union; KPS: Karnofsky Performance Status; TTF: tumor treating fields.

^a Medical therapy included bevacizumab, irinotecan, nitrosoureas, platinum-based chemotherapy (ie, carboplatin); temozolomide; or a combination of procarbazine, chloroethyl ether, and vincristine.

Participants were followed monthly, including laboratory tests. MRI images were evaluated at 2, 4, and 6 months from initiation of treatment, with subsequent MRIs performed according to local practice until disease progression. QOL questionnaires were completed every 3 months. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess mortality rates. The primary end point was OS. Secondary end points included PFS, the percentage of patients with PFS at 6 months, time to progression, 1-year survival rate, QOL, and radiologic response. All end points were evaluated using intention-to-treat analysis.

The trial did not reach its primary end point of improved survival compared with active medical therapy (see Table 6). With a median follow-up of 39 months, 93% of patients had died. There

was not a statistically significant difference in survival rates at 1, 2, and 3 years between groups. Patients in the TTF group did not, however, suffer the typical systemic side effects of chemotherapy. The most common adverse event in the TTF group was grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids and did not require treatment breaks. Control participants experienced grade 2, 3, or 4 events by organ system related to the pharmacologic activity of chemotherapy agents used. Hematologic events of grade 2 or greater were observed in 17% of chemotherapy patients compared with 3% of TTF patients. Gastrointestinal disorders of grade 2 or greater were identified in 17% of chemotherapy patients compared with 4% of TTF patients. Severe (grades 3-4) hematologic and gastrointestinal toxicity was observed in 7% of chemotherapy controls compared with 1% of the TTF group.

Longitudinal QOL data, available in 63 (27%) participants, showed no meaningful differences between groups for the domains of global health and social functioning. However, cognitive and emotional functioning domains favored TTF therapy. Symptom scale analysis was by treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration.

The trial had a number of limitations (see Tables 7 and 8), that included lack of blinding and high loss to follow-up. Discontinuation of TTF therapy occurred in 22% of patients due to noncompliance or inability to handle the device, usually within the first few days. In the control group, 21 (18%) patients did not return to the treatment site, and details on disease progression and toxicity were not available. Longitudinal QOL could be analyzed only for 27% of patients who remained on study therapy for 3 months. The trial was designed as a superiority trial and did not provide adequate evidence of noninferiority.

Table 6. Summary of Key Randomized Controlled Trial Results for Recurrent or Progressive Glioblastoma

| Study; Trial | LTFU, n (%) | Median OS, mo | Progression-Free Survival | | Overall Survival (95% CI), % | | |
|-----------------------------------------|-------------|---------------------|---------------------------|------------------------------|------------------------------|-------------|------------|
| | | | Median, mo | Rate at 6 Months (95% CI), % | 1 Year | 2 Years | 3 Years |
| Stupp et al (2012) ⁴ ; EF-11 | | | | | | | |
| TTF | 23 (22) | 6.6 | 2.2 | 21.4 (13.5 to 29.3) | 20 | 8 (4 to 13) | 4 (1 to 8) |
| PCC | 12 (18) | 6.0 | 2.1 | 15.1 (7.8 to 22.3) | 20 | 5 (3 to 10) | 1 (0 to 3) |
| HR (95% CI) | | 0.86 (0.66 to 1.12) | 0.81 (0.60 to 1.09) | | | | |
| P value | | 0.27 | 0.16 | 0.13 | | | |

CI: confidence interval; HR: hazard ratio; LTFU: loss to follow-up; PCC: physician's choice chemotherapy; TTF: tumor treating fields.

Table 7. Relevance Gaps

| Study | Population ^a | Intervention ^b | Comparator ^c | Outcomes ^d | Follow-Up ^e |
|-----------------------------------------|-------------------------|---------------------------|------------------------------------|-----------------------|------------------------|
| Stupp et al (2012) ⁴ ; EF-11 | | | 2. Physician's choice chemotherapy | | |

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^aPopulation key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^bIntervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^a Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Gaps

| Study; Trial | Allocation ^a | Blinding ^b | Selective Reporting ^d | Data Completeness ^e | Power ^d | Statistical ^f |
|-----------------------------------------|-------------------------|----------------------------------------|-------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-------------------------------------------|
| Stupp et al (2012) ⁴ ; EF-11 | | 1. Not blinded to treatment assignment | | 1. 78% of TTF group completed only 1 cycle of therapy, 18% of control group lost to follow-up 1. Longitudinal QOL data were available for 27% of patients | | 1. Not designed as a noninferiority trial |

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. QOL: quality of life.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Nonrandomized Comparative Studies

Kesari et al (2017) conducted a post hoc analysis of the EF-14 trial (see Stupp et al [2017] above) to evaluate the efficacy of TTF in patients who had the first recurrence.¹³ Some patients in the temozolomide alone group crossed over to receive TTF plus chemotherapy after the first recurrence, resulting in 144 patients who received TTF fields plus chemotherapy and 60 patients who received chemotherapy alone for recurrent GBM (see Table 9). Patient characteristics and second-line treatments were well-balanced between the groups, with bevacizumab the most common second-line therapy. The median OS in patients treated with systemic therapy alone was 9.2 months (see Table 10). In comparison, the group of patients who received TTF therapy in addition to systemic therapy had a median OS of 11.8 months ($p=0.043$).

A registry study published Mrugala et al (2014) assessed OS data from patients who received NovoTTF therapy in a real-world, clinical practice setting (see Table 9).¹⁴ Concurrent treatment was not captured in the registry, and it is possible that some patients received combination therapy. Median OS in the PRiDe clinical practice dataset (9.6 mo) was reported as superior to that attained in the EF-11 pivotal trial (6.6 mo, $p<0.001$) (see Table 10). More patients in the PRiDe registry were treated for first recurrence (33% vs 9%), and more had received bevacizumab as prior therapy (55% vs 19%). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

Table 9. Characteristics of Key Nonrandomized Trial Results

| Study | Study Type | Country | Dates | Participants | TTF | Controls | FU |
|------------------------------------|-------------------------|---------------------------------|-----------|-------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------|---------|
| Kesari et al (2017) ¹³ | EF-14 post hoc analysis | U.S., E.U., South Korea, Israel | 2009-2016 | 204 patients with first recurrence in the EF-14 trial | 144 patients treated with TTF plus second-line chemotherapy | 60 patients treated with second-line chemotherapy | 12.6 mo |
| Mrugala et al (2014) ¹⁴ | Registry | U.S. (91 centers) | 2011-2013 | 457 patients with recurrent GBM | Patient Registry Dataset (PRiDe) | EF-11 | |

FU: follow-up; GBM: glioblastoma; TTF: tumor treating fields.

Table 10. Summary of Key Nonrandomized Trial Results

| Study | Median OS, mo | Median OS With Bevacizumab, mo | | |
|-------------------------------------------|---------------------|--------------------------------|--|--------------|
| Kesari et al (2017) ¹³ ; EF-14 | | | | |
| TTF plus chemotherapy | 11.8 | 11.8 | | |
| Chemotherapy alone | 9.2 | 9.0 | | |
| Hazard ratio (95% CI) | 0.70 (0.48 to 1.00) | 0.61 (0.37 to 0.99) | | |
| P value | 0.049 | 0.043 | | |
| | | 1-Year OS, % | | 2-Year OS, % |
| Mrugala et al (2014) ¹⁴ | | | | |
| PRiDe Registry | 9.6 | 44 | | 30 |
| EF-11 | 6.6 | 20 | | 9 |
| Hazard ratio (95% CI) | 0.66 (0.05 to 0.86) | | | |
| P value | <0.001 | | | |

CI: confidence interval; OS: overall survival; TTF: tumor treating fields.

Post hoc analyses of the EF-11 pivotal trial have been reported. Wong et al (2014) published a subgroup analysis to determine characteristics of responders and nonresponders in the active treatment and active treatment control.¹⁵ They found that responders had a lower grade of histology and lower daily dexamethasone use than nonresponders. A second post hoc analysis by Kanner et al (2014) of the EF-11 pivotal trial data was performed to evaluate OS among patients who finished at least 1 complete course of TTF or chemotherapy.¹⁶ The investigators reported that median OS was 7.7 months in the TTF group compared with 5.9 months in the chemotherapy group ($p=0.009$). These post hoc analyses are considered to be hypothesis-generating.

Section Summary: TTF Therapy as an Adjunct or Alternative to Chemotherapy for Progressive or Recurrent GBM

The single RCT for TTF as an alternative to chemotherapy reported that outcomes following TTF therapy were similar to outcomes following standard chemotherapy. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. The noninferiority of TTF compared with chemotherapy might be considered a sufficient health benefit, if TTF reduced treatment toxicity. However, because the trial was not designed as a noninferiority trial no inferences of noninferiority compared with chemotherapy can be made. Physician's choice therapy during the trial was heterogeneous, although analysis indicated that survival was not affected by choice of chemotherapy. More patients in the TTF group than in the control group did not complete the treatment course. The number of patients who contributed QOL data was approximately one-quarter of total enrollment, and the self-reported QOL indicators might have been subject to bias due to the lack of blinding.

A nonrandomized post hoc evaluation of the EF-14 trial suggests that TTF may improve survival when combined with chemotherapy for recurrent GBM. This analysis should be considered hypothesis-generating, and further study in high-quality RCTs is needed.

SUMMARY OF EVIDENCE

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes an RCT. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 3 physician specialty societies (one of which provided 6 responses and 2 of which provided 1 response each) and 1 academic medical center (total of 9 individual responses) while this policy was under review in 2016. There was majority support, but not consensus, for the use of tumor treatment fields therapy as an adjunct to maintenance treatment following initial therapy for glioblastoma multiforme. There was mixed

support for the use of tumor treatment fields as an alternative to chemotherapy in advanced or recurrent glioblastoma multiforme.

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2018) include recommendations for the treatment of glioblastoma (see Table 11).³ For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate O⁶-methylguanine-DNA methyltransferase promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric field therapy is a category 1 recommendation. Alternating electric currents therapy is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a category 2B recommendation.

Table 11. Guidelines for Adjuvant Treatment of Glioblastoma, by Age and Performance Status

| * Age, y | KPS Score, % | Treatment Options | Category |
|----------|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| ≤70 | ≥60 | <ul style="list-style-type: none"> • Standard RT plus concurrent and adjuvant temozolomide plus TTF • Standard RT plus concurrent and adjuvant temozolomide | 1 |
| ≤70 | <60 | <ul style="list-style-type: none"> • Hypofractionated RT with/without concurrent or adjuvant temozolomide • Temozolomide • Palliative/best supportive care | 2A |
| >70 | ≥60 | <ul style="list-style-type: none"> • Hypofractionated RT plus concurrent and adjuvant temozolomide • Standard RT plus concurrent and adjuvant temozolomide plus TTF • Temozolomide alone • Hypofractionated brain RT alone | 1 |
| >70 | <60 | <ul style="list-style-type: none"> • Hypofractionated brain RT alone • Temozolomide alone • Palliative/best supportive care | 2A |

KPS: Karnofsky Performance Status; RT: radiotherapy; TTF: tumor treating fields.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 12. Of particular note are the phase 3 trials evaluating TTF therapy in non-small-cell lung cancer and pancreatic cancer. TTF therapy is an active area of research for mechanisms underlying its effects on cancer cells.

Table 12. Summary of Key Trials

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|--------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------------------|
| Ongoing | | | |
| NCT01971281 ^a | A Phase II Study of TTFields (150 kHz) Concomitant With Gemcitabine and TTFields Concomitant With Gemcitabine Plus Nab-paclitaxel for Front-line Therapy of Advanced Pancreatic Adenocarcinoma | 40 | Dec 2017 (ongoing) |
| NCT01894061 ^a | A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma | 40 | Dec 2018 |
| NCT02663271 ^a | A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the Combination of TTFields and Pulsed | 18 | Mar 2019 |

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------------|
| | Bevacizumab Treatment in Patients With Bevacizumab-refractory Recurrent Glioblastoma | | |
| NCT02831959 ^a | Pivotal, Open-label, Randomized Study of Radiosurgery With or Without Tumor Treating Fields (TTFields) (150kHz) for 1-10 Brain Metastases From Non-small Cell Lung Cancer (NSCLC) (METIS) | 270 | Jul 2019 |
| NCT02973789 ^a | LUNAR: Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields) Concurrent With Standard of Care Therapies for Treatment of Stage 4 Non-small Cell Lung Cancer (NSCLC) Following Platinum Failure | 534 | Dec 2021 |
| NCT02743078 ^a | Phase II Trial Of Optune® Plus Bevacizumab In Bevacizumab-Refractory Recurrent Glioblastoma | 85 | Aug 2022 |
| NCT03377491 ^a | EF-27 Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields, 150kHz) Concomitant With Gemcitabine and Nab-paclitaxel for Front-line Treatment of Locally-advanced Pancreatic Adenocarcinoma (PANOV-3) | 556 | Dec 2022 |

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.**CODING**

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

| | |
|-------|--------------------------------------------------------------------------------------------------------------|
| A4555 | Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only |
| E0766 | Electrical stimulation device, used for cancer treatment, includes all accessories, any type |

ICD-10 Diagnoses

| | |
|-------|-------------------------------------------------------------|
| C71.0 | Malignant neoplasm of cerebrum, except lobes and ventricles |
| C71.1 | Malignant neoplasm of frontal lobe |
| C71.2 | Malignant neoplasm of temporal lobe |
| C71.3 | Malignant neoplasm of parietal lobe |
| C71.4 | Malignant neoplasm of occipital lobe |
| C71.5 | Malignant neoplasm of cerebral ventricle |
| C71.6 | Malignant neoplasm of cerebellum |
| C71.7 | Malignant neoplasm of brain stem |
| C71.8 | Malignant neoplasm of overlapping sites of brain |

REVISIONS

| | |
|------------|--------------------------------------------------------|
| 08-01-2018 | Policy added to the bcbsks.com web site on 08-01-2018. |
|------------|--------------------------------------------------------|

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Medical Policy



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Joint Medical Policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and is therefore subject to change.

***Current Policy Effective Date: 5/1/18**

(See policy history boxes for previous effective dates)

Title: Tumor-Treatment Fields Therapy for Glioblastoma

Description/ Background

Glioblastoma multiforme is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during the course of treatment. Tumor-treatment fields (TTF) therapy is a new, noninvasive technology that is intended to treat glioblastoma using electrical fields.

The Optune device has been approved by the FDA to treat patients with newly-diagnosed glioblastoma multiforme (GBM), an aggressive form of brain cancer. It is given along with the chemotherapy drug temozolomide (TMZ) following standard treatments that include surgery, and a combination of radiation therapy and chemotherapy when used together.

The FDA based its approval of the expanded indication of the Optune device on results from a clinical trial involving 695 patients newly diagnosed with GBM that compared those who used Optune with TMZ to those receiving TMZ alone. Patients who used the device along with TMZ lived, on average, about seven months with no disease progression and survived for an average of 19.4 months after starting treatment. Those who were only treated with TMZ, lived, on average four months with no disease progression and survived for an average of 16.6 months after starting treatment.

In the clinical study used to support the expanded indication, patients treated with the device and TMZ lived on average three months longer than those treated with the drug alone.

BACKGROUND

Glioblastoma Multiforme

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults, and they comprise approximately 15% of all brain and central nervous system tumors and more than 50% of all tumors that arise from glial cells.(1)

The peak incidence for GBM occurs between the ages of 45 and 70 years. GBMs are grade IV astrocytomas, the most deadly type of glial cell tumor, and are often resistant to standard chemotherapy.(1) According to the National Comprehensive Cancer Network, GBM is the "most lethal brain tumor with only a third of patients surviving for 1 year and less than 5% living beyond 5 years."(2)

Treatment of Glioblastoma Multiforme

The primary treatment for patients newly diagnosed with GBM is to resect the tumor, confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. At that time, some patients may undergo implantation of the tumor cavity with a carmustine (BCNU)-impregnated wafer.(2) Depending on the patient's physical condition, adjuvant radiation therapy, chemotherapy (typically temozolomide), or a combination of the two are sometimes given. After adjuvant therapy, some patients may undergo maintenance therapy with temozolomide. Prognostic factors for success of therapy are age, histology, and performance status or physical condition of the patient.

No standard treatment exists for recurrent GBM. In patients with disease that recurs after initial treatment, additional debulking surgery may be used if recurrence is localized. Other treatment options for recurrent disease include various forms of systemic medications such as bevacizumab, bevacizumab plus chemotherapy (eg, irinotecan, BCNU/chloroethylnitrosourea [CCNU], temozolomide), temozolomide, nitrosourea, PCV (procarbazine, CCNU, vincristine), cyclophosphamide, and platinum-based agents.(2) External beam radiotherapy (EBRT) also may be used to treat recurrent GBM.

Fractionated external-beam radiotherapy after surgery is standard adjuvant therapy and may be used to treat recurrent GBM. Response rates in recurrent disease are less than 10%, and progression-free survival rates at 6 months are less than 20%. (2,3)

Tumor Treatment Field Therapy

TTF therapy is a new, noninvasive technology that is intended to treat GBM on an outpatient basis using electrical fields. (3-5) TTF therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively inhibit tumor growth and reduce tumor angiogenesis. TTF are proposed to inhibit rapidly dividing tumor cells by two mechanisms; arrest of cell proliferation and destruction of cells while undergoing division. (4,5)

Optune, formerly NovoTTF-100A™ System, is the only legally marketed TTF delivery system available in the United States. Optune is a portable device that generates alternating electrical fields within the body (called tumor treatment fields). The fields are conducted via disposable electrode patches that are attached to the patient's shaved scalp, over the site of the tumor. (3,4) The device is used by the patient at home on a continuous basis (20-24 hours per day) for the duration of treatment, which can last for several months. Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living. (6)

Regulatory Status

The NovoTTF-100A™ System (assigned the generic name of TTF) was approved by FDA in April 2011 through the premarket approval process. (7) The FDA-approved label reads as

follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed GBM, following histologically or radiologically confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment, and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."(7)

In September 2014, FDA approved Novocure's request to change its product name from NovoTTF-110A System to Optune™. (8)

In October 2015, FDA expanded the indication for Optune™ in combination with temozolomide to include newly diagnosed glioblastoma.(6) The device was granted priority review status in May 2015 because there was no legally marketed alternative device currently available for the treatment of newly diagnosed GBM that represents a life-threatening condition.

Optune was initially approved in 2011, by the FDA, to treat patients with GBM that recurred or progressed after chemotherapy. With the 2015 expanded indication, Optune™ can be used as part of a standard treatment for GBM before the disease progresses. For newly diagnosed GBM, Optune™ is not intended to be used as a substitute for standard treatments, but rather as an adjunct therapy.

For newly diagnosed GBM, Optune™ is given along with the chemotherapy drug temozolomide (TMZ) following standard treatments that include surgery and the combination of radiation and chemotherapy. Optune™ should not be used without a physician's supervision. Patients should not use Optune™ if they have an active implanted medical device, a skull defect or known sensitivity to conductive hydrogels, such as those used on electrocardiogram stickers. (21)

Medical Policy Statement

The safety and effectiveness of tumor-treatment fields (TTF) therapy has been established. It is a useful therapeutic option for patients meeting specific selection criteria.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:

Tumor treatment field therapy may be medically necessary when prescribed by a physician for the treatment of newly diagnosed, histologically confirmed supratentorial glioblastoma multiforme in:

- Adults (22 years of age and older) **AND**
- When used as an adjunct therapy to standard treatments that include maximal debulking surgery and completion of radiation together with the chemotherapy drug temozolomide (TMZ)

OR

- For adults 22 years of age and older with reoccurrence of histologically or radiologically confirmed supratentorial glioblastoma multiforme, the Tumor Treatment Fields may be used as monotherapy as an alternative to standard medical therapy

Exclusions:

Tumor treatment field therapy is considered investigational/experimental:

- Combined with chemotherapy other than TMZ
- When used for any indications other than those listed above

CPT/ HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

| | | |
|-------|-------|-------|
| A4555 | E0766 | 95999 |
|-------|-------|-------|

Other codes (investigational, not medically necessary, etc.):

| | | |
|-------|-------|-------|
| E1399 | A9900 | 77299 |
|-------|-------|-------|

Rationale

Re-radiation options are limited for glioblastoma (GBM) patients who have received initial external-beam radiotherapy due to radiation tolerances. The tumors are locally invasive but do not metastasize, therefore, tumor treating fields (TTF) therapy as a locoregional intervention is proposed to treat GBM. For this review, 2 indications will be considered: (1) TTF as an alternative to chemotherapy in progressive or recurrent GBM and (2) TTF as an adjunct to maintenance treatment in patients following initial treatment. Comparative trials are essential to determine efficacy in this area, and randomized controlled trials (RCTs) are needed to control for heterogeneity in the patient populations and other confounders of outcome. This review will include both RCTs and nonrandomized comparative trials.

TTF AS AN ALTERNATIVE TO CHEMOTHERAPY FOR PROGRESSIVE OR RECURRENT GBM

Randomized Controlled Trials

The U.S. Food and Drug Administration (FDA) approval of the NovoTTF-100A system was based on a phase 3, multinational prospective randomized controlled trial (RCT) (EF11) which was published in 2012 by Stupp et al. The Stupp study, which was sponsored and funded by the manufacturer of the device (Novocure), compared TTF therapy (delivered by the NovoTTF-100A System) with the best standard of care chemotherapy (active control). Twenty-eight clinical centers (across 7 countries) enrolled 237 adult participants with relapsed or progressive glioblastoma multiforme (GBM), despite conventional radiotherapy. Other prior treatments may have included surgery and/or chemotherapy. Patient characteristics were balanced in both groups, with median age of 54 years and median Karnofsky Performance Status score of 80%. More than 80% of participants had failed 2 or more prior chemotherapy regimens (\geq second recurrence), and 20% had failed bevacizumab prior to study enrollment.

Two hundred thirty-seven patients were randomized in a 1:1 ratio to receive TTF therapy only (n=120) or active control (n=117). The choice of chemotherapy regimens varied, reflecting local practice at each of the participating clinical centers. Chemotherapy agents considered as active control during the trial included platinum-based chemotherapy (ie, carboplatin); nitrosureas; procarbazine; combination of procarbazine, lomustine and vincristine (PCV); temozolomide; and bevacizumab. For patients assigned to the TTF group, uninterrupted treatment was recommended, although patients were allowed to take treatment breaks of up to 1 hour, twice per day, for personal needs (eg, shower). In addition, patients assigned to the TTF group were allowed to take 2 to 3 days off treatment at the end of each of 4-week period (which is the minimal required treatment duration for TTF therapy to reverse tumor growth). A period of 28 days of treatment with TTF was considered 1 full treatment course.

The study was designed as a superiority trial. The primary study end point in this RCT was overall survival (OS).(3) Secondary end points included progression-free survival (PFS) at 6 months, time to progression, 1-year survival rate, quality of life (QOL), and radiological response. All end points were evaluated using intention-to-treat analysis. Participants were seen in clinic monthly, and magnetic resonance imaging (MRI) was performed after 2, 4, and 6 months from initiation of treatment, with subsequent MRIs done according to local practice until disease progression. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with the participants' caregivers were used to assess mortality rates.

Ninety-seven percent (116) of 120 participants in the TTF group started treatment and 93 participants (78%) completed 1 cycle (4 weeks) of therapy. Discontinuation of TTF therapy occurred in 27 participants (22%) due to noncompliance or the inability to handle the device.(3) For each TTF treatment month, the median compliance was 86% (range, 41%-98%), which equaled a mean use of 20.6 hours per day. In the active control group, 113 (97%) of the 117 assigned participants received chemotherapy and all except 1 individual completed a full treatment course. Twenty-one participants (18%) in the active control group did not return to the treating site and details on disease progression and toxicity were not available.

We summarize study outcomes in Table 1.

Table 1. Randomized Trial of TTF Versus Physicians' Choice Chemotherapy in Recurrent Glioblastoma: Principal Efficacy Results From Stupp et al

| Outcomes | TTF | Chemotherapy | Measure of Association, Significance |
|--------------------------------------------------|-----|--------------|----------------------------------------|
| Median survival, mo | 6.6 | 6.0 | |
| Hazard ratio survival | | | 0.86 (95% CI, 0.66 to 1.12) favors TTF |
| Radiologic response (not all patients evaluated) | 14% | 9.6% | p=0.19 |
| Median PFS, mo | 2.2 | 2.1 | |
| Hazard ratio PFS | | | 0.81 (95% CI, 0.60 to 1.09) favors TTF |

CI: confidence interval; PFS: progression-free survival; TTF: tumor treatment fields.

The trial did not reach its primary end point of improved survival compared to active chemotherapy. With a median follow-up of 39 months, 220 participants (93%) had died. Median survival was 6.6 months in the TTF group compared to 6.0 months in the active control group (hazard ratio, 0.86; 95% confidence interval [CI], 0.66 to 1.12; p=0.27). For both groups, 1-year survival was 20%. The survival rates for 2- and 3-year survival were 8% and 4%, respectively, for the TTF group versus 5% and 1%, respectively, for the active control group. PFS rate at 6 months was 21.4% in the TTF group, compared to 15.1% in the active control

group ($p=0.13$). Objective radiological responses (partial and complete response) were noted in 14 participants in the TTF group and 7 in the active control group, with a calculated response rate of 14.0% (95% CI, 7.9% to 22.4%) compared to 9.6% (95% CI, 3.9% to 18.8%), respectively. Sixteen percent of the TTF participants had grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids. Active control participants experienced grade 2-4 events by organ system related to the pharmacologic activity of chemotherapy agents utilized; severe (grades 3 and 4) toxicity was observed in 3% of participants.

Longitudinal QOL data were available in 63 participants (27%). There were no meaningful differences observed between the groups in the domains of global health and social functioning. However, cognitive, emotional, and role functioning favored TTF therapy; physical functioning favored chemotherapy. Symptom scale analysis was in accordance to treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the TTF group.

Wong et al published a subgroup analysis of the Stupp RCT (previously described) to determine characteristics of responders and nonresponders in the treatment and active control groups.⁽⁹⁾ Tumor response was assessed by the Macdonald criteria. More patients in the TTF arm were considered responders (14/120 vs 7/117 in the chemotherapy arm.) Median response time was longer for those in the TTF arm than the chemotherapy arm (7.3 months vs 5.6 months, $p<0.001$), and there was a strong correlation (Pearson's r) between response and OS in the TTF arm ($p<0.001$) but not in chemotherapy arm ($p=0.29$). Compared with the chemotherapy arm, a higher proportion of responders in the TTF arm had a prior low-grade histology (36% vs 0%). These differences in treatment responder groups suggest that TTF therapy may differentially benefit certain types of GBM; however, the small numbers of responders in both groups limits generalizations that can be drawn from this analysis.

A second post hoc analysis of the TTF EF-11 pivotal trial data was performed to evaluate OS rates among patients who completed at least 1 complete course of TTF or chemotherapy. ⁽¹⁰⁾ Investigators analyzed survival in what they referred to as a "modified ITT [intention-to-treat]" subgroup comprising 93 of 120 (78%) of the original TTF allocated group, versus 117 of 117 (100%) of the original chemotherapy allocated group. This exercise revealed median OS of 7.7 months in the TTF modified ITT (mITT) group compared with 5.9 months in the chemotherapy group (HR=0.69; 95% CI, 0.52 to 0.91; $p=0.009$). They also showed a trend relationship between proportion of patients with higher TTF compliance and median OS rates ($p=0.039$). The investigators suggest that TTF provides an OS benefit if used as intended in the FDA-approved label when compared with best chemotherapy. This post hoc analysis is limited as it was not prespecified in the study, includes only 78% of the original TTF allocated patients, and fails to control for noncompliance due to faster clinical deterioration of TTF recipients leading to treatment cessation.

Noncomparative Studies

Two nonrandomized studies were identified that compared TTF treatment with standard care using historical controls. A study published in late 2014 included OS data from 457 patients included in the Patient Registry Dataset (PRiDe), a postmarketing registry of all recurrent GBM patients who received NovoTTF therapy in a real-world, clinical practice setting in 91 centers in the United States between October 2011 and November 2013.⁽¹¹⁾ The median OS rate in the PRiDe clinical practice dataset was reported as significantly superior to that attained in the TTF

EF-11 pivotal trial (9.6 months vs 6.6 months; HR=0.66, 95% CI, 0.05 to 0.86; p<0.001). One- and 2-year OS rates for TTF in PRiDe were significantly longer than those in the TTF group in the EF-11 trial (44% vs 20% at 1 year; 30% vs 9% at 2 years, respectively). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

Kirson et al (2007) reported the findings of a study examining the effects of TTF therapy delivered by the NovoTTF-100A System in 10 patients with recurrent glioblastoma multiforme (GBM).(12) Median time to progression (TTP) in these patients was 26.1 weeks and median overall survival (OS) was 62.2 weeks. The authors noted that these TTP and OS values were more than double the reported medians of historical control patients. No device-related serious adverse events were seen after more than 70 months of cumulative treatment in all of the patients. The only device-related adverse event observed was a mild-to-moderate contact dermatitis beneath the field delivering electrodes. The primary limitation of this study was the use of historical controls, since the patients included may not be comparable on major clinical and prognostic features.

Two small case series have been published of long-term survival (>6 years) with TTF therapy.(14,15) Rulseh et al reported long-term (>7 year) survival in 4 of 20 patients with GBM who were treated with TTF,(14) while Villano et al describe 1 patient with recurrent GBM who was tumor-free more than 6 years after treatment with TTF.(15)

Section Summary: TTF Therapy as an Alternative to Chemotherapy for Progressive or Recurrent GBM

Multiple case reports and small case series have concluded that TTF treatments are similar to outcomes following standard chemotherapy, with a decrease in toxicity and increase in quality of life favoring TTF.(16) Although global health and social functioning didn't show meaningful differences, cognitive, emotional and role functioning favored TTF therapy. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the TTF group.

Treatment-associated toxicity such as appetite loss, diarrhea, constipation, nausea and vomiting were directly related to the chemotherapy administration, but not reported with the TTF. The most common side effect reported during TTF treatment was a mild-to-moderate contact dermatitis beneath the field delivering electrodes. Overall, TTF yielded a longer OS in recurrent and advance GBM when compared to chemotherapy. TTF appears to provide an OS benefit when used as intended per the FDA approval.

TTF THERAPY AS AN ADJUNCT TO STANDARD MAINTENANCE CARE FOR GBM

In 2015, Stupp et al published a planned interim analysis of a multicenter, open-label RCT that evaluated maintenance therapy with TTF for GBM. (13) This trial enrolled patients with GBM who had completed standard treatment consisting of biopsy or surgical resection followed by chemoradiotherapy with temozolomide. A Karnofsky Performance Status score of 70% or higher was an additional inclusion criterion. Patients were randomized in a 2:1 fashion to TTF plus temozolomide or to temozolomide alone. At the time of the interim analysis, 210 patients were randomized to TTF plus temozolomide and 105 patients to temozolomide alone. The primary outcome was PFS analyzed by intention-to-treat; a secondary outcome was OS analyzed by per-protocol analysis.

Patients in the TTF group received continuous TTF therapy delivered mainly in the home setting. Patients were trained on use of the device, including changing the electrodes, and then

treatment continued at home. Patients were encouraged to wear the device continuously, with the exception of short breaks to attend to personal needs. All patients were seen monthly for follow-up. Further, MRI was performed every 2 months and QOL measures administered every 3 months. Tumor progression was adjudicated by a central review committee blinded to treatment group.

Planned interim analysis was performed at a median follow-up of 38 months (range, 18-60 months). Median PFS and median OS are summarized in Table 2.

Table 2. TTF Therapy as an Adjunct to Standard Maintenance Care in Glioblastoma Multiforme

| Group | N | Progression-Free Survival (95% CI), mo | Hazard Ratio (98.7% CI) | Overall Survival (95% CI), mo | Hazard Ratio (99.4% CI) |
|--------------------|-------------------------|----------------------------------------|-------------------------|-------------------------------|-------------------------|
| TTF + temozolomide | 210 (196 ^a) | 7.1 (5.9 to 8.2) | 0.62 (0.43 to 0.89) | 20.5 (16.7 to 25) | 0.64 (0.42 to 0.98) |
| Temozolomide alone | 105 (84 ^a) | 4.0 mo (3.3 to 5.2) | | 15.6 mo (13.3 to 19.1) | |

CI: confidence interval; TTF: tumor treatment fields.

^a Included in per-protocol analysis.

There were 35 (11%) dropouts during the trial - 14 (6.7%) of 210 patients in the TTF group and 21 (20%) of 105 in the temozolomide-alone group. Adherence to treatment was defined as wearing the device for at least 18 hours a day, and 157 (75%) of 210 patients met this adherence criterion. The number of treatment cycles with temozolomide differed between groups. The TTF group received a median of 6 cycles compared with a median of 4 cycles for the temozolomide-alone group. The most common side effect of treatment was local skin irritation, which occurred in 43% of patients treated with TTF.

In October 2014, the trial independent data and safety monitoring committee reviewed the interim analysis, concluding that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended trial termination. The FDA approved study termination and the trial was closed to recruitment that November after 695 of the planned 700 participants had been randomized. All patients in the control maintenance therapy arm could crossover to receive TTFs. At the time of the Stupp interim analysis, 35 control arm participants had crossed over. FDA considered the results of this analysis for the 2015 expanded approval of Optune.

Section Summary: TTF Therapy as an Adjunct to Standard Maintenance Care for GBM

The single RCT for this indication reports that PFS is improved by 3.1 months and OS is improved by 4.9 months after the addition of TTF to standard maintenance therapy (ie, temozolomide). Therefore, there may be a survival benefit associated with TTF for this indication.

SUMMARY OF EVIDENCE

The evidence for tumor-treatment field therapy in patients who have recurrent or progressive glioblastoma multiforme includes 1 randomized controlled superiority pivotal trial using the U.S. Food and Drug Administration– approved device and a number of small observational studies. Relevant outcomes include overall survival (OS), quality of life (QOL), and treatment-related morbidity. GBM is the most common brain tumor, has a low quality of life during the course of treatment and has a poor prognosis. TTF therapy offers a noninvasive approach to newly diagnosed and recurrent tumors. In 2011 the FDA approved TTF therapy for use in recurrent

tumors. In 2015 the FDA expanded its recommendations for use in newly diagnosed GBM which meet specified criteria.

Studies indicated that patients treated with the device and TMZ had a longer progression-free survival of 3.1 months and an overall survival of 4.9 months longer than those who were treated with only TMZ. For individuals who have advanced or recurrent GBM and receive TTF as an alternative to standard chemotherapy, no difference was noted in overall survival.

Furthermore, there is consensus within the National Comprehensive Cancer Network that indicates consideration of alternating electric field therapy in the treatment of a recurrent glioblastoma brain tumor is appropriate.

The use of TTF therapy has been described in a number of case series. High quality studies are difficult to obtain related to the mortality rate associated with GBM. Published studies indicate that some patients who underwent TTF therapy achieved long-term survival of > 5-7 years. TTF therapy appeared to offer a higher survival rate than chemotherapy alone with the only side effect being contact dermatitis of the scalp; thus, offering a better outcome through increased quality and quantity of life.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------------|
| Ongoing | | | |
| NCT01894061 ^a | A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma | 40 | Dec 2017 |
| NCT01756729 ^a | A Prospective, Non-randomized, Concurrent Control, Open Label, Post-approval Study of NovoTTF-100A in Recurrent GBM Patient | 486 | Jan 2018 |
| NCT02743078 ^a | Phase II Trial Of Optune® Plus Bevacizumab In Bevacizumab-Refractory Recurrent Glioblastoma | 85 | Apr 2018 |
| NCT01954576 | A Phase II Study of the NovoTTF-100A system, Enhanced by Genomic Analysis to Identify the Genetic Signature of Response in the Treatment of Recurrent Glioblastoma Multiforme | 30 | May 2018 |
| NCT02663271 ^a | A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the Combination of TTFields and Pulsed Bevacizumab Treatment in Patients With Bevacizumab-refractory Recurrent Glioblastoma | 25 | May 2018 |
| NCT02893137 ^a | Phase 1 Enhancing Optune Therapy of Recurrent Glioblastoma Multiforme Using Targeted Surgical Skull Remodeling | 15 | Oct 2019 |
| NCT01925573 ^a | Proposed Pilot Study of Combined Optune+ Bevacizumab, and Hypofractionated Stereotactic Irradiation for Bevacizumab-Naive Recurrent Glioblastoma | 27 | Dec 2021 |

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

Supplemental Information

CLINICAL INPUT RECEIVED FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests for input on the use of TTF for treatment of GBM in 2016, BCBSA received input from 1 academic medical center and 3 physician specialty societies, with a total of 9 individual responses. There was majority support, but not consensus, for use of TTF as an adjunct to maintenance treatment following initial therapy for GBM. There was mixed support for use of TTF as an alternative to chemotherapy in advanced or recurrent GBM.

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2016) (2) include a recommendation for the treatment of glioblastoma. For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate MGMT promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric currents therapy is a category 2A recommendation. Alternating electric currents therapy is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a 2B recommendation.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

Government Regulations

National:

There is no national coverage determination for TTF.

Local:

Tumor Treatment Field Therapy

L34823; Effective: October 2015, Revised 1/1/17

Tumor treatment field therapy (E0766) will be denied as not reasonable and necessary.

A52711 Effective date: 10/01/15, Revised 1/1/17

NON-MEDICAL NECESSITY COVERAGE AND PAYMENT RULES:

For any item to be covered by Medicare, it must 1) be eligible for a defined Medicare benefit category, 2) be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member, and 3) meet all other applicable Medicare statutory and regulatory requirements.

Information provided in this policy article relates to determinations other than those based on

Social Security Act §1862(a)(1)(A) provisions (i.e. "reasonable and necessary"). TUMOR TREATMENT FIELD therapy devices are covered under the Durable Medical Equipment benefit (Social Security Act §1861(s)[6]). In order for a beneficiary's equipment to be eligible for reimbursement the reasonable and necessary (R&N) requirements set out in the related Local Coverage Determination must be met. In addition, there are specific statutory payment policy requirements, discussed below, that also must be met.

Code E0766 is in the frequent and substantial service payment category. Items included in this payment category are reimbursed a single monthly fee schedule amount for the device and all related supplies and accessories. Separate billing of supplies and/or accessories will be denied as unbundling.

Code A4555 is not valid for billing to Medicare. If code A4555 is billed, it will be denied as an invalid code.

Michigan Department of Health & Human Services:

Codes E0766 and A4555 are not listed on the MDHHS DME POS fee schedule.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 10/05/2017, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

| Policy Effective Date | BCBSM Signature Date | BCN Signature Date | Comments |
|-----------------------|----------------------|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 7/1/14 | 4/8/14 | 4/15/14 | Joint policy established |
| 9/1/15 | 6/19/15 | 7/16/15 | Routine review |
| 5/1/16 | 2/16/16 | 2/23/16 | <ul style="list-style-type: none"> • Updated to reflect new FDA indications (2015); • Diverge from BCBSA; • Converted from Investigational to Mixed (per new FDA indications); • Codes added to inclusions and exclusions |
| 5/1/17 | 3/8/17 | 3/16/17 | <ul style="list-style-type: none"> • Routine maintenance • 95199 added – placement of Novo-Tal pads • Continue to diverge from BCBSA • References and rationale updated |
| 5/1/18 | 2/20/18 | 2/20/18 | <ul style="list-style-type: none"> • Routine maintenance |

Next Review Date: 1st Qtr, 2019

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: TUMOR-TREATMENT FIELDS THERAPY FOR GLIOBLASTOMA

I. Coverage Determination:

| | |
|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Commercial HMO (includes Self-Funded groups unless otherwise specified) | Covered; criteria apply |
| BCNA (Medicare Advantage) | Refer to the Medicare information under the Government Regulations section of this policy. |
| BCN65 (Medicare Complementary) | Coinsurance covered if primary Medicare covers the service. |

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.

| | |
|-----------------|--------------------------------|
| Medical Policy: | II-164-003 |
| Topic: | Tumor Treatment Fields Therapy |
| Section: | Medicine |
| Effective Date: | March 27, 2017 |
| Issue Date: | March 27, 2017 |
| Last Reviewed: | March 2017 |

Tumor treatment fields (TTF) therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency. The use of TTF is proposed to inhibit rapidly dividing tumor cells by arresting cell proliferation, leading to destruction of cells.

Optune™ (formerly known as the NovoTTF-100A™ System) received premarket approval (PMA) from the U.S. Food and Drug Administration (FDA) in 2011 as a treatment for adult patients (22 years of age or older) with confirmed glioblastoma multiforme (GBM), following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment, and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted. In October 2015, the FDA approved the Optune™ with temozolomide for the treatment of adult patients (22 years of age or older) with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

Glioblastoma is also known as glioblastoma multiforme (GBM). The term "multiforme" is no longer part of the World Health Organization (WHO) designation, though glioblastoma is still often abbreviated "GBM." Glioblastoma is the most common form of malignant primary brain tumor in adults, and comprises approximately 15% of all brain and central nervous system tumors. Glioblastoma is a WHO grade IV astrocytoma, the most deadly type of glial cell tumor, which is often resistant to standard chemotherapy.

Tumor treatment fields therapy for glioblastoma is delivered by a battery-powered, portable device that generates the electrical fields via disposable electrodes that are noninvasively attached to the patient's shaved scalp over the site of the tumor. The device is used by the patient at home on a continuous basis (20-24 hours per day) for the duration of treatment, which can last for several months. The use of TTF is also under investigation for several other types of malignancies, including cancers of the breast, lung, ovaries and pancreas, as well as melanoma and solid tumor brain metastases.

This policy is designed to address medical guidelines that are appropriate for the majority of individuals with a particular disease, illness, or condition. Each person's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

Policy Position Coverage is subject to the specific terms of the member's benefit plan.

EXHIBIT 1. PAGE 816

I. Tumor treatment fields (TTF) therapy may be considered **MEDICALLY NECESSARY** for patients who meet **ALL** of the following criteria:

- History of histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma); **AND**
- Recurrence of glioblastoma in the supratentorial region of the brain has been histologically or radiologically confirmed; **AND**
- After surgery, radiation and chemotherapy, or patient is not a candidate for these treatments.

II. Tumor treatment fields (TTF) therapy is considered **INVESTIGATIVE** for all other indications including, but not limited to treatment of other malignancies (e.g., cancers of the breast, lung, ovaries, pancreas, melanoma and solid tumor brain metastases). There is a lack of evidence demonstrating an impact on improved health outcomes for treatment of conditions other than recurrent glioblastoma.

Procedure Codes

A4555, E0766

Denial Statements

No additional statements.

Links

Blue Cross and Blue Shield of Minnesota medical policies apply generally to all Blue Cross and Blue Plus plans and products. Benefit plans vary in coverage and some plans may not provide coverage for certain services addressed in the medical policies.

Medicaid products and some self-insured plans may have additional policies and prior authorization requirements. As applicable, review the provisions relating to a specific coverage determination, including exclusions and limitations. Note that services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial of claims may result if criteria are not met.

For Medicare NCD and/or Medicare LCD, please consult CMS or National Government Services websites.

Blue Cross and Blue Shield of Minnesota reserves the right to revise, update and /or add to its medical policies at any time without notice. Codes listed on this policy are included for informational purposes only, and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. These guidelines are the proprietary information of Blue Cross and Blue Shield of Minnesota. Any sale, copying or dissemination of the medical policies is prohibited; however, limited copying of medical policies is permitted for individual use.

Corporate Medical Policy

Tumor-Treatment Fields Therapy

File Name: tumor_treatment_fields_therapy
Origination: 9/2013
Last CAP Review: 11/2017
Next CAP Review: 11/2018
Last Review: 6/2018

Description of Procedure or Service

Tumor-treatment fields therapy is a noninvasive technology that uses alternating electrical fields. It is used to treat glioblastoma multiforme, and has been proposed for use in other tumor types.

Background

Glioblastoma, also known as glioblastoma multiforme (GBM), is the most common form of malignant primary brain tumor in adults, comprising approximately 15% of all brain and central nervous system tumors and more than 50% of all tumors that arise from glial cells. The peak incidence for GBM occurs between the ages of 45 and 70 years. GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor, which is often resistant to standard chemotherapy. According to the National Comprehensive Cancer Network (NCCN), GBM is the "deadliest brain tumor with only a third of patients surviving for one year and less than 5% living beyond 5 years."

The primary treatment for newly diagnosed GBM is debulking surgery to remove as much of the tumor as possible. At the time of surgery, some patients may undergo implantation of the tumor cavity with a carmustine (BCNU) -impregnated wafer. Depending on the patient's physical condition, adjuvant radiation therapy, chemotherapy (typically temozolomide), or a combination of the two is recommended. After adjuvant therapy, some patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles.

No standard treatment exists for recurrent GBM. In patients with disease that recurs after these initial therapies, additional debulking surgery may be used if recurrence is localized. Other treatment options for recurrent disease include various forms of systemic medications such as bevacizumab, bevacizumab plus chemotherapy (e.g., irinotecan, BCNU/CCNU, temozolomide), temozolomide, nitrosourea, PCV (procarbazine, CCNU, and vincristine), cyclophosphamide, and platinum-based agents. External beam radiotherapy also may be used to treat recurrent GBM. Response rates in recurrent disease are less than 10%, and progression-free survival rates at 6 months are less than 20%.

Tumor-treatment fields (TTF) therapy is a noninvasive technology that is intended to treat GBM on an outpatient basis using electrical fields. TTF therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively inhibit tumor growth and reduce tumor angiogenesis. Tumor-treatment fields are proposed to inhibit rapidly dividing tumor cells by two mechanisms, arrest of cell proliferation and destruction of cells while undergoing division.

The NovoTTF-100A™ System (Novocure Ltd., Haifa, Israel) has been approved by the U.S. Food and Drug Administration (FDA) to deliver TTF therapy. TTF therapy via the NovoTTF-

Tumor-Treatment Fields Therapy

100A™ System is delivered by a battery-powered, portable device that generates the fields via disposable electrodes that are noninvasively attached to the patient's shaved scalp over the site of the tumor. The device is used by the patient at home on a continuous basis (20–24 hours per day) for the duration of treatment, which can last for several months. Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living.

Regulatory Status

The NovoTTF-100A™ System (assigned the generic name of tumor-treatment fields) was approved by the FDA in April 2011 through the premarket approval process. The FDA-approved indication for use is: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment, and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, FDA approved a request for Novocure to change its products name from Novo-TTF-110A System to Optune™.

In October 2015, FDA expanded the indication for Novocure's use of Optune in combination with temozolomide for newly diagnosed glioblastoma.

Related Policies

Analysis of MGMT Promoter Methylation in Malignant Gliomas

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for tumor treatment fields therapy when it is determined to be medically necessary because the medical criteria shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Tumor-Treatment Fields Therapy is covered

Tumor treatment fields (TTF) therapy is considered to be **medically necessary** for the treatment of newly diagnosed, supratentorial glioblastoma multiforme, as an adjunct to standard maintenance therapy with temozolomide when **ALL** of the following conditions are met:

- The patient has completed initial treatment with surgery, radiation therapy and concomitant chemotherapy; **AND**
- The patient is ≥ 18 years of age; **AND**
- Has a Karnofsky Performance Status score $\geq 70\%$; **AND**
- There is documentation of lack of tumor progression following radiation and chemotherapy (see Policy Guidelines); **AND**
- The individual is willing and capable of wearing the device for at least 18 hours a day.

Tumor-Treatment Fields Therapy

When Tumor-Treatment Fields Therapy is not covered

Tumor treatment fields therapy (TTF) is considered investigational, including, but not limited to, the following situations:

- As an alternative or an adjunct to standard medical therapy (eg bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme.
- In the treatment of other types of malignant tumors, including but not limited to, pancreatic adenocarcinoma, lung cancer and brain metastases.

Policy Guidelines

In the EF-14 trial, tumor progression following radiochemotherapy was defined as 25% or more increase in enhancing lesions or any new lesions, as determined by imaging.

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment with surgery, radiotherapy, and/or chemotherapy who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes an RCT. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: A4555, E0766

Tumor-Treatment Fields Therapy

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual [Electronic Version], 1.01.29, 8/8/2013

Specialty Matched Consultant – 9/2013

Senior Medical Director – 9/2013

Specialty Matched Consultant Advisory Panel – 11/2013

BCBSA Medical Policy Reference Manual [Electronic Version], 1.01.29, 8/14/14

Specialty Matched Consultant Advisory Panel – 11/2014

BCBSA Medical Policy Reference Manual [Electronic Version], 1.01.29, 8/13/15

Specialty Matched Consultant Advisory Panel- 11/2015

BCBSA Medical Policy Reference Manual [Electronic Version], 1.01.29, 8/11/16

Specialty Matched Consultant Advisory Panel- 11/2016

BCBSA Medical Policy Reference Manual [Electronic Version], 1.01.29, 7/13/17

Specialty Matched Consultant Advisory Panel- 11/2017

BCBSA Medical Policy Reference Manual [Electronic Version], 1.01.29, 6/14/18

Medical Director review 6/18/18

Policy Implementation/Update Information

For Policy Titled: Tumor-Treatment Fields Therapy for Glioblastoma

10/1/13 New policy. Tumor treatment fields therapy to treat glioblastoma is considered investigational. Senior Medical Director review 8/30/2013. Specialty Matched Consultant review 9/18/2013. (btw)

12/10/13 Specialty Matched Consultant Advisory Panel review 11/20/2013. No change to policy statement. (btw)

12/31/13 Added new HCPCS codes, A4555 and E0766, to the Billing/Coding section. Removed the following statement from the Billing/Coding section; "Providers will most likely use E1399 and A9900 for claim submission." (btw)

12/9/14 Specialty Matched Consultant Advisory Panel review 11/24/2014. No change to policy intent. Reference added. (lpr)

Tumor-Treatment Fields Therapy

- 12/30/15 Updated Policy Guidelines. Specialty Matched Consultant Advisory Panel review 11/18/2015. Reference added. No change to policy statement. (lpr)
- 12/30/16 Updated Policy Guidelines, Description and Regulatory status. Clarified non-covered indications. Reference added. Medical Director review 9/2016. Specialty Matched Consultant Advisory Panel review 11/30/2016. No change to policy intent. (lpr)
- 8/11/17 Updated Policy Guidelines section. Clarified policy statement: 1) as an alternative to standard chemotherapy for patients with progressive or recurrent glioblastoma multiforme after initial or repeat treatment with surgery, radiotherapy, and/or chemotherapy; 2) as an adjunct to standard maintenance therapy in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy and/or chemotherapy. No change to policy intent and the service remains investigational. Reference added. (lpr)
- 8/25/17 Under "When Not Covered" section: clarified investigational indications. No change to policy intent. (lpr)
- 12/15/17 Specialty Matched Consultant Advisory Panel review 11/29/2017. No change to policy statement. (lpr)

For Policy Titled: Tumor-Treatment Fields Therapy

- 06/29/18 Updated Description and Policy Guidelines sections. Under "When Covered section, revised policy statement to reflect medical necessity coverage for the treatment of newly diagnosed, supratentorial glioblastoma multiforme, as an adjunct to standard maintenance therapy with temozolomide when **ALL** of the following conditions are met: The patient has completed initial treatment with surgery, radiation therapy, and concomitant chemotherapy; **AND**; The patient is ≥ 18 years of age; **AND**; Has a Karnofsky Performance Status score $\geq 70\%$; **AND**; There is documentation of lack of tumor progression following radiation and chemotherapy (see Policy Guidelines); **AND**; the individual is willing and capable of wearing the device for at least 18 hours a day. **Title changed from "Tumor-Treatment Fields Therapy for Glioblastoma" to "Tumor-Treatment Fields Therapy.** Reference added. Medical Director review 6/18/18. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.

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Category:

Tumor Treatment Fields (TTF)

Section: Durable Medical Equipment**Effective Date:** November 1, 2018**Issued Date:** September 26, 2018

Electrical fields, known as “tumor treatment fields” (TTF), are created by low-intensity, alternating intermediate frequency (100-200 kilohertz [kHz]) electric currents delivered to the malignant tumor site by insulated electrodes placed on skin surface of the tumor site. As a result of the unique shape and electrical characteristics of dividing tumor cells, TTF exposure may damage the dividing cells through anti-microtubule mechanisms and could stop tumor growth while sparing normal tissue.

Policy Position

TTF may be considered medically necessary when **ALL** of the following indications are met:

- When it is used as an alternative to standard medical therapy, as a monotherapy; **and**
- For treatment of adult patients (22 years of age or older); **and**
- With histologically-confirmed glioblastoma multiforme; **and**
- Following histologically- or radiologically-confirmed recurrence in the Supratentorial region of the brain; **and**
- After receiving chemotherapy; **and**
- After surgical and radiation options have been exhausted.

OR

TTF may be considered medically necessary when **ALL** of the following indications are met:

- It is used as an adjunct to standard maintenance therapy; **and**
- For treatment for adult patients (22 years of age or older); **and**
- With histologically-confirmed glioblastoma multiforme; **and**
- When it is used with temozolomide; **and**
- With newly diagnosed, supratentorial glioblastoma, **and**
- Following maximal debulking surgery; **and**
- Completion of radiation therapy; **and**
- Together with concomitant standard of care chemotherapy.

TTF is considered experimental/investigational when above criteria are not met or for any other indications, and therefore, not covered because the safety and/or effectiveness of this service cannot be established by the available published peer-reviewed literature.

Procedure Codes

A4555, E0766

Covered Diagnosis Codes for Procedure Codes A4555 and E0766

| | |
|-------|-------------------------------------------------------------|
| C71.0 | Malignant neoplasm of cerebrum, except lobes and ventricles |
| C71.1 | Malignant neoplasm of frontal lobe |
| C71.2 | Malignant neoplasm of temporal lobe |
| C71.3 | Malignant neoplasm of parietal lobe |
| C71.4 | Malignant neoplasm of occipital lobe |
| C71.5 | Malignant neoplasm of cerebral ventricle |
| C71.6 | Malignant neoplasm of cerebellum |
| C71.7 | Malignant neoplasm of brain stem |
| C71.8 | Malignant neoplasm of overlapping sites of brain |
| C71.9 | Malignant neoplasm of brain, unspecified |

Place of Service: Inpatient/Outpatient

Experimental/Investigational (E/I) services are not covered regardless of place of service.

The use of tumor treatment fields is typically an outpatient procedure which is only eligible for coverage as an inpatient procedure in special circumstances, including, but not limited to, the presence of a co-morbid condition that would require monitoring in a more controlled environment such as the inpatient setting.

Denial Statements

Services that do not meet the criteria of this policy will be considered experimental/investigational (E/I). A network provider can bill the member for the experimental/investigational service. The provider must give advance written notice informing the member that the service has been deemed E/I. The member must be provided with an estimate of the cost and the member must agree in writing to assume financial responsibility in advance of receiving the service. The signed agreement must be maintained in the provider's records.

Links

- [Reference \(pdf\)](#)

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EFFECTIVE DATE: 10|01|2018
POLICY LAST UPDATED: 08|07|2018

OVERVIEW

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

MEDICAL CRITERIA

BlueCHiP for Medicare and Commercial Products:

Tumor treating fields therapy to treat glioblastoma multiforme is considered medically necessary as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy when **all** of the following criteria are met:

- Adult patients ≥ 18 years of age
- Supratentorial tumor
- Karnofsky Performance Status score $\geq 70\%$ *
- Patient understands device use, including the requirement for a shaved head, and is willing to comply with the Food and Drug Administration label guideline to use Optune for at least 18 hours a day and should finish at least 4 full weeks of therapy to get the best response to treatment.

APPROVAL PERIOD: 6 months. Services beyond the 6 months will need a new review and meet the above criteria.

*KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

- 100 Normal no complaints; no evidence of disease.
- 90 Able to carry on normal activity; minor signs or symptoms of disease. Able to carry on normal activity and to work; no special care needed.
- 80 Normal activity with effort; some signs or symptoms of disease.
- 70 Cares for self; unable to carry on normal activity or to do active work.
- 60 Requires occasional assistance, but is able to care for most of his personal needs. Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.
- 50 Requires considerable assistance and frequent medical care.
- 40 Disabled; requires special care and assistance.
- 30 Severely disabled; hospital admission is indicated although death not imminent.
- 20 Very sick; hospital admission necessary; active supportive treatment necessary.
- 10 Moribund; fatal processes progressing rapidly. Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.
- 0 Dead

PRIOR AUTHORIZATION

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MEDICAL COVERAGE POLICY | 1

Prior authorization is required for BlueCHiP for Medicare and recommended for Commercial Products

POLICY STATEMENT

BlueCHiP for Medicare and Commercial Products:

Tumor treating fields therapy is medically necessary when the above criteria is met.

BlueCHiP for Medicare

Tumor treating fields therapy is considered not covered in all other conditions, including but not limited to the following situations:

- As an adjunct to standard medical therapy (eg, bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
- For brain metastases
- For cancer in areas other than the brain.

Commercial Products:

Tumor treating fields therapy is considered not medically necessary in all other conditions, including but not limited to the following situations:

- As an adjunct to standard medical therapy (eg, bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
- For brain metastases
- For cancer in areas other than the brain.

COVERAGE

Benefits vary between groups/contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for services not medically necessary or not covered

BACKGROUND

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes a randomized controlled trial (RCT). Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in

chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

CODING

BlueCHiP for Medicare and Commercial Products

The following code is medically necessary/covered when criteria is met.

E0766: Electrical stimulation device used for cancer treatment, includes all accessories, any type

The following code is covered when the service is approved

A4555: Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only

RELATED POLICIES

None

PUBLISHED

Provider Update, September 2018

Provider Update, September 2017

Provider Update, October 2016

Provider Update, April 2015

Provider Update, March 2014

REFERENCES

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CAM 042 Electric Tumor Treatment Field (TTF)

Category: Radiology Last Reviewed: July 2013

Department(s): Medical Affairs Next Review: July 2014

Original Date: July 2013

Description:

Electrical fields known as "tumor treatment fields (TTF)" are created by low-intensity, alternating intermediate frequency (100 – 200 kilohertz [kHz]) electric currents delivered to the malignant tumor site by insulated electrodes placed on skin surface of the tumor site. As a result of the unique shape and electrical characteristics of dividing tumor cells, TTF exposure may damage the dividing cells through anti-microtubule mechanisms and could stop tumor growth while sparing normal tissue.

Policy:

The use of devices to generate electric tumor treatment fields (ETTF) is **MEDICALLY NECESSARY** as monotherapy for persons with histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma), after histologically or radiologically confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy.

The use of devices to generate electric tumor treating fields (TTF) as a treatment for malignant tumors is considered **INVESTIGATIONAL** for all other indications.

Rationale:

The use of electric fields and the corresponding effects upon living tissue has been studied in the laboratory and clinical settings. Alternating electric fields at very low frequencies (below one kHz) stimulate excitable tissue resulting from membrane depolarization (Kirson 2004, 2007, 2009; Salzberg, 2008). Electric fields in the tens of kHz to megahertz (intermediate-frequency) alternate too fast to stimulate tissue and results in minute heating. Kirson and colleagues (2004) demonstrated targeted inhibitory effects on dividing cells with the application of alternating electric fields of very low-intensity (less than two V/centimeter [cm]) and intermediate-frequency, called TTF. Utilizing time-lapse microphotography of mouse melanoma cell cultures, unique cellular processes as a result of TTF

exposure were identified. Prolongation of mitosis in TTF-treated cells was statistically significant, and one quarter of the treated cells was destroyed. Cellular destruction was observed only in mitotic cells, and cells at rest (quiescent) remained intact, both functionally and morphologically. Nuclear rotation was also observed in TTF treated cell cultures. Microtubules, in the form of spatially organized mitotic spindles in dividing cells, have very large electric dipole moments that may be disoriented by TTF forces. In the control cell cultures, 95 percent of the mitotic spindles were intact and exhibited normal features in cells undergoing mitosis compared to 50 percent of abnormal cell activity in TTF-treated cultures. The use of TTF was then applied in vivo, to two animal tumor models (adenocarcinoma and malignant melanoma cells). TTF-treated tumors were significantly smaller compared to the control tumor size, and the surrounding normal tissue was spared from injury. The encouraging preclinical data led to studies of electric TTF treatment in humans.

The U.S. Food and Drug Administration (FDA, 2011) approved NovoTTF-100A System (NovoCure Ltd., Haifa, Israel) as a treatment for adults with histologically-confirmed, recurrent glioblastoma multiforme (GBM) in the supratentorial region of the brain, based on data presented to the committee from a phase III, multinational, randomized, controlled pivotal clinical trial. Twenty-eight clinical centers enrolled 237 adult participants with relapsed or progressive GBM despite conventional therapy (e.g., surgery and chemo-radiotherapy followed by hemotherapy). One hundred twenty participants were randomized in a 1:1 ratio to receive NovoTTF treatment and 117 participants were randomized to the BSC group with effective chemotherapies as practiced at each of the participating clinical centers. Chemotherapy agents considered as BSC during the trial included platinum-based chemotherapy (i.e., carboplatin); nitrosureas (BCNU); procarbazine; combination of procarbazine, lomustine and vincristine (PCV); temozolomide; and bevacizumab. A period of twenty-eight-days of treatment with NovoTTF was considered one full treatment course. Participants treated with NovoTTF were allowed to take breaks from treatment up to an hour, twice per day for personal needs such as showers. The primary endpoint of the study was overall survival (OS). Secondary endpoints included progression free survival rates at 6-months (PFS6); time to progression (TTP), 1-year survival rate; quality of life (QOL); and radiological response. Participants were seen in clinic monthly, and magnetic resonance imaging (MRI) was performed after 2, four and six months from initiation of treatment and subsequent MRIs were done according to local practice until disease progression. Medical follow-up continued for two months after disease progression. Monthly telephone interviews with the participants' caregivers were used to assess participant mortality rates.

Of the 237 enrollees, eight participants (4 in each group) did not receive the assigned therapy. Ninety-7 percent (116) of 120 enrollees in the NovoTTF group started treatment and 93 participants (78 percent) completed one cycle (4 weeks) of therapy. Discontinuation of TTF occurred in 27 participants due to noncompliance or the inability to handle the device. For each TTF treatment month, the median compliance was 86 percent (range 41-98 percent), which equaled a mean use of 20.6 hours per day. In the BSC (active control) group, 113 (97 percent) of the 117 assigned participants received chemotherapy and all completed one full treatment course with the exception of one individual. In the BSC cohort, 21 participants did not return to the site and details on disease progression and toxicity were not available. Stupp and colleagues (2012) noted the median survival of 6.6 months in the TTF group was marginally higher than six months in the BSC group (hazard ratio 0.86 [95 percent confidence interval [CI] 0.66 – 1.12]; $p=0.27$). For both groups, one-year survival was 20 percent. The survival rates for 2- and 3-years were 8 percent (95 percent CI 4, 13) and 4 percent (95 percent CI 1, 8) versus 5 percent (95 percent CI 3, 10) and 1 percent (95 percent CI 0, 3) for the TTF cohort compared to the BSC cohort, respectively. With a median follow-up of 39 months, 93 percent (220 participants) had died. Objective radiological responses (partial and complete response) were noted in 14 participants in the TTF group and seven in the BSC group, with a calculated response rate of 14.0 percent (95 percent CI 7.9- 22.4 percent) compared to 9.6 percent (95 percent CI 3.9 – 18.8 percent), respectively. Sixteen percent of the TTF participants had grade one and two contact

dermatitis on the scalp, which resolved with topical steroids. BSC participants experienced grade 2-4 events by organ system related to the pharmacologic activity of chemotherapy agents utilized. Quality of life data were available in 63 participants (27 percent). Based on the QLQ C-30 and BN-20 questionnaires (5 out of six general scales and of nine symptom seven scales including nausea, vomiting, diarrhea, constipation and pain, quality of life was consistently higher in NovoTTF than in the control group. There were no meaningful differences observed between the domains of global health and social functioning. The BSC cohort had a larger decrease in the negative effects of seizures than the TTF cohort. The self-reporting of QOL indicators may be influenced by bias for the treatment group (FDA Label, 2011; Stupp, 2012).

In an industry-sponsored study, Kirson and colleagues (2007) reported results of TTF treatment on various tumor cell lines and animal tumor models and noted "optimal frequencies differed between cancer cell types." Additionally, the effects of a total of 280 weeks of TTF treatment on 10 individuals with recurrent GBM were reported in the pilot study. TTF treatment resulted in a median TTP of 26.1 weeks (range three – 124 weeks) and the PFS6 months of 50 percent (23 -77 percent confidence interval). The median OS is 62.2 weeks (range 20.3 - 124.0 weeks). One individual achieved a CR and is free from tumor ten months after stopping treatment, and one participant achieved and continues to maintain a PR seven months after stopping treatment. The authors concluded "TTF treatment is encouraging when compared to historical average PFS6 of 15.3 ± 3.8 percent and average historical TTP of 9.5 ± 1.6 weeks and an average OS $29.3 \pm$ six weeks. Mild to moderate contact dermatitis was reported in nine out of ten participants.

In 2009, results from a pilot study of TTF alone and TTF in combination with chemotherapy for individuals with diagnosed GBM were reported (Kirson). In this single arm study, the first group included 10 individuals with recurrent GBM after failure of maintenance temozolomide (Kirson, 2007), and 10 individuals with newly diagnosed GBM treated with TTF combined with temozolomide were in the second cohort. All 20 individuals were treated for an average of one year (range 2.5 – 24 months) continuously. The first group was compared to a matched group of 18 concurrent controls who received salvage chemotherapy for relapsed/recurrent GBM. The TTF-chemotherapy group was compared to a matched group of 32 concurrent controls who received temozolomide alone. In addition, OS for both cohorts was compared to matched historical control data. Data for the first group were reported in 2007 (Kirson). For the group of 10 individuals with newly diagnosed GBM, PFS was significantly different ($P = .0002$, HR 3.32 [95 percent CI 1.9 – 5.9]) between the TTF-chemotherapy group compared to the matched concurrent and historical controls. The difference in OS was also significant ($P=0.0018$). The authors concluded TTF may also be an effective sensitizer when used concurrently with chemotherapeutic agents.

A pilot study (Salzberg, 2008) included six participants with locally advanced or metastatic malignant tumors (3 cases - skin metastasis from primary breast cancer; one case each: GBM, malignant melanoma, mesothelioma). Participants had no concomitant anti-tumor therapy and had no additional standard therapy available. All six participants had a total of 128 full days of TTF treatment with individual exposure of 13 – 46 days. Compliance was greater than 80 percent. Three out of six participants had grade one skin irritation which was reversible with electrode repositioning and application of topical steroid ointments. A partial response in skin metastasis from primary breast cancer was observed in one participant. Tumor growth was arrested in three participants and one participant had progressive disease. The participant with mesothelioma had stabilization of a portion of the tumor while another part of the tumor had progressive disease. The individual with GBM did not respond to four weeks of treatment. The mixed results and minimal toxicities from TTF warranted "further investigation in larger clinical trials."

Although the NovoTTF-100A device has received FDA approval, the pivotal trial did not achieve the primary endpoint of the study, which was improved survival with NovoTTF treatment in comparison to chemotherapy. In

addition, the long-term safety and efficacy as a treatment for recurrent GBM has not been demonstrated. The expedited premarket approval (PMA) includes a requirement for a post-market non-randomized, unblinded, concurrent control study of NovoTTF-100A in individuals with recurrent GBM. The primary question to be addressed by the study (FDA Label, 2011): "Is the overall survival of patients treated with NovoTTF-100A non-inferior to the survival of patients treated with the best standard of care (chemotherapy)?" There are currently ongoing clinical trials investigating the safety and effectiveness of the novel TTF device. In addition, there are ongoing investigations to determine the optimal TTF dosing for specific tumor types; the use of TTF alone and in combination with chemotherapy agents; and its place in therapy. Currently, published articles include animal studies, in vitro studies and small case series.

Treatment recommendations published by the National Comprehensive Cancer Network[®] (NCCN, 2012) and the National Cancer Institute (NCI, 2012) include surgical resection, radiation therapy and/or chemotherapy as treatment options, and do not include TTF treatment for recurrent GBM.

The NovoTTF-100A System was approved by the U.S. Food and Drug Administration in April, 2011. This novel device was approved to treat adults with glioblastoma multiforme (GBM) that recurs or progresses after receiving chemotherapy and radiation therapy. TTF technology is also being studied as a treatment for other solid tumors such as non-small cell lung cancer and melanoma. There are published data from TTF use to treat tumors in pre-clinical trials and from small case series. However, there is a paucity of published evidence from randomized controlled trials comparing the long term safety and efficacy of TTF as a treatment of tumors.

According to the National Cancer Institute, glioblastoma (World Health Organization grade IV) is also known as glioblastoma multiforme (GBM). The peak incidence for GBM occurs between the ages of 45 and 70 years. Glioblastoma is highly invasive and is the most frequently occurring brain tumor accounting for approximately 12 percent to 15 percent of all brain tumors and 50 percent to 60 percent of all astrocytic tumors. Giant cell glioblastoma and gliosarcoma are two histologic variants of glioblastoma multiforme. According to the NCCN (2012) GBM is the "deadliest brain tumor with only a third of patients surviving for one year and less than 5 percent living beyond five years."

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BlueCross BlueShield of Vermont

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Tumor Treatment Fields for CNS Cancers Corporate Medical Policy

File Name: Tumor Treatment Fields for CNS Cancers

File Code: UM.SPSVC.22

Origination: New policy

Last Review: 06/2018

Next Review: 06/2019

Effective Date: 10/01/2018

Description/Summary

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

Policy

Coding Information

Click the links below for attachments, coding tables & instructions.

Attachment 1

When a service may be considered medically necessary

Tumor treating fields therapy to treat glioblastoma multiforme, anaplastic oligodendroglioma, anaplastic astrocytoma, and anaplastic gliomas may be considered **medically necessary**, in the following situations:

- As an alternative to standard chemotherapy for patients with progressive or recurrent glioblastoma multiforme, anaplastic oligodendroglioma, anaplastic astrocytoma, and anaplastic gliomas after initial or repeat treatment with surgery, radiotherapy, and/or chemotherapy when disease is unresectable or resection not recommended.
- As adjuvant treatment to standard therapy in patients with supratentorial disease and glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy.

When a service is considered investigational

Tumor treating fields therapy is considered investigational for ALL other indications.

Policy Guidelines

There are no specific codes for the initial application of this system or instruction on use. The patient reapplies the transducer arrays at home after the initial instruction.

Reference Resources

1. Blue Cross Blue Shield Association Medical Policy Reference Manual. Tumor Treatment Fields Therapy for Glioblastoma. 1.01.29. 7:2017.
2. National Cancer Institute (NCI). Adult Central Nervous System Tumors Treatment (PDQ®)-Health Professional Version 1 2018.
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Document Precedence

Blue Cross and Blue Shield of Vermont (BCBSVT) Medical Policies are developed to provide clinical guidance and are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. The applicable group/individual contract and member certificate language, or employer's benefit plan if an ASO group, determines benefits that are in effect at the time of service. Since medical practices and knowledge are constantly evolving, BCBSVT reserves the right to review and revise its medical policies periodically. To the extent that there may be any conflict between medical policy and contract/employer benefit plan language, the member's contract/ employer benefit plan language takes precedence.

Audit Information

BCBSVT reserves the right to conduct audits on any provider and/ or facility to ensure compliance with the guidelines stated in the medical policy. If an audit identifies instances of non-compliance with this medical policy, BCBSVT reserves the right to recoup all non-compliant payments.

Administrative and Contractual Guidance

Benefit Determination Guidance

Prior approval is required and benefits are subject to all terms, limitations and conditions of the subscriber contract.

Incomplete authorization requests may result in a delay of decision pending submission of missing information. To be considered complete, see policy guidelines above.

An approved referral authorization for members of the New England Health Plan (NEHP) is required. A prior approval for Access Blue New England (ABNE) members is required. NEHP/ ABNE members may have different benefits for services listed in this policy. To confirm benefits, please contact the customer service department at the member's health plan.

Federal Employee Program (FEP): Members may have different benefits that apply. For further information please contact FEP customer service or refer to the FEP Service Benefit Plan Brochure. It is important to verify the member's benefits prior to providing the service to determine if benefits are available or if there is a specific exclusion in the member's benefit.

Coverage varies according to the member's group or individual contract. Not all groups are required to follow the Vermont legislative mandates. Member Contract language takes precedence over medical policy when there is a conflict.

If the member receives benefits through an Administrative Services Only (ASO) group, benefits may vary or not apply. To verify benefit information, please refer to the member's employer benefit plan documents or contact the customer service department. Language in the employer benefit plan documents takes precedence over medical policy when there is a conflict.

Policy Implementation/Update information

| | |
|---------|-----------------------------------------------------------------------|
| 06/2018 | New Policy, input received from external network specialty providers. |
|---------|-----------------------------------------------------------------------|

Eligible providers

Qualified healthcare professionals practicing within the scope of their license(s).

Approved by BCBSVT Medical Director(s)

Date Approved

Joshua Plavin, MD, MPH, MBA
Chief Medical Officer

Attachment I

| Code Type | Number | Brief Description | Policy Instructions |
|---------------------------------------------------------------------------------------------------|--------|--------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| The following codes are considered as medically necessary when applicable criteria have been met. | | | |
| HCPCS | A4555 | Electrode/ transducer for use with electrical stimulation device used for cancer treatment, replacement only | Prior Approval Required if over the following dollar threshold per contract. |
| HCPCS | E0766 | Electrical stimulation device used for cancer treatment, includes all accessories, any type | Requires Prior Approval |

Protocol

Tumor Treating Fields Therapy

(10129)

(Formerly Tumor Treatment Fields Therapy for Glioblastoma)

| | | | |
|------------------|-----|-------------------------------------------------|-------------------------|
| Medical Benefit | | Effective Date: 10/01/18 | Next Review Date: 07/19 |
| Preauthorization | Yes | Review Dates: 09/15, 05/16, 09/16, 09/17, 07/18 | |

Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

| Populations | Interventions | Comparators | Outcomes |
|------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Individuals: <ul style="list-style-type: none">• With newly diagnosed glioblastoma multiforme on maintenance therapy after initial treatment | Interventions of interest are: <ul style="list-style-type: none">• Tumor treating fields therapy as an adjunct to standard maintenance therapy | Comparators of interest are: <ul style="list-style-type: none">• Standard maintenance therapy alone | Relevant outcomes include: <ul style="list-style-type: none">• Overall survival• Disease-specific survival• Quality of life• Treatment-related morbidity |
| Individuals: <ul style="list-style-type: none">• With progressive or recurrent glioblastoma multiforme | Interventions of interest are: <ul style="list-style-type: none">• Tumor treating fields therapy as an adjunct or alternative to medical therapy | Comparators of interest are: <ul style="list-style-type: none">• Standard medical therapy | Relevant outcomes include: <ul style="list-style-type: none">• Overall survival• Disease-specific survival• Quality of life• Treatment-related morbidity |

DESCRIPTION

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

SUMMARY OF EVIDENCE

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes a randomized controlled trial (RCT). Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (i.e., temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited.

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The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

Tumor treating fields therapy to treat glioblastoma multiforme is considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:

- Adult patients ≥ 22 years of age
- Supratentorial tumor
- Karnofsky Performance Status score $\geq 70\%$
- Patient understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the Food and Drug Administration label (see Policy Guidelines).

Tumor treating fields therapy is considered **investigational** in all other conditions, including but not limited to the following situations:

- As an adjunct to standard medical therapy (e.g., bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
- For brain metastases
- For cancer in areas other than the brain.

POLICY GUIDELINES

Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth $> 25\%$ compared with the smallest tumor area measured in the patient during the trial or appearance of one or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).

The Food and Drug Administration label includes the following notices:

- Patients should use Optune for at least 18 hours a day to get the best response to treatment
- Patients should finish at least four full weeks of therapy to get the best response to treatment. Stopping treatment before four weeks lowers the chances of a response to treatment.

MEDICARE ADVANTAGE

For Medicare Advantage tumor-treatment fields therapy is considered **not medically necessary**.

BACKGROUND

GLIOBLASTOMA MULTIFORME

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.¹ GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (e.g., bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors.¹ The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to one year, and the five-year survival rate was around 5%.²

Clinical Context and Therapy Purpose

The purpose of alternating electrical field therapy, more commonly known as TTF therapy, is to provide a treatment option that is better than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

Treatment of Newly Diagnosed GBM

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these two therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for five days of every 28-day cycle for six cycles. Response and overall survival rates with temozolomide are higher in patients who have O6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation.

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice.³ For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur essentially all patients.

Treatment of Recurrent GBM

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivascular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (e.g., lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at six months is less than 20%.⁴ There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

The questions addressed in this protocol are:

- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

Interventions

TTF therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields.⁴⁻⁶ TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. TTF therapy is proposed to inhibit tumor growth by two mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase.^{5,6} Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune (formerly NovoTTF-100A System) is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma,⁴ disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and two to three days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is one month, with the continuation of treatment available until recurrence.

Comparators

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

The following practices are currently being used to make decisions about recurrent GBM: medical therapy.

TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds three to five months.⁴

Outcomes

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

Timing

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.

Setting

The setting is outpatient care by an oncologist or neuro-oncologist.

REGULATORY STATUS

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process.⁷ The FDA-approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, the FDA approved Novocure's request for a product name change from NovoTTF-110A System to Optune®.⁸

In October 2015, the FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.⁹ The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

FDA product code: NZK.

RELATED PROTOCOLS

Intensity-Modulated Radiotherapy: Central Nervous System Tumors

Intracavitary Balloon Catheter Brain Brachytherapy for Malignant Gliomas

Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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WYOMING

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Corporate Medical Policy

Title: Tumor Treating Fields Therapy Policy # 1.01.29.0

Last Review: July 2018

Next Review: July 2019

POLICY DISCLAIMER

Current medical policy is to be used in determining a Member's contract benefits on the date that services are rendered. Contract language, including definitions and specific inclusions/ exclusions, as well as state and federal law, must be considered in determining eligibility for coverage. Members must consult their applicable benefit plans or contact a Member Services representative for specific coverage information. Likewise, medical policy, which addresses the issue(s) in any specific case, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving and the Company reserves the right to review and update medical policy periodically.

Tumor Treating Fields Therapy

| Populations | Interventions | Comparators | Outcomes |
|---------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| Individuals: • With newly diagnosed glioblastoma multiforme on maintenance therapy after initial treatment | Interventions of interest are: • Tumor treating fields therapy as an adjunct to standard maintenance therapy | Comparators of interest are: • Standard maintenance therapy alone | Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity |
| Individuals: • With progressive or recurrent glioblastoma multiforme | Interventions of interest are: • Tumor treating fields therapy as an adjunct or alternative to medical therapy | Comparators of interest are: • Standard medical therapy | Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity |

Summary

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes a randomized controlled trial (RCT). Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were not-blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

OBJECTIVE

The objective of this evidence review is to determine whether the use of tumor treating fields therapy improves the net health outcome for patients with solid tumors including glioblastoma multiforme.

POLICY

Tumor treating fields therapy to treat glioblastoma multiforme is considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:

- Adult patients ≥ 18 years of age
- Supratentorial tumor
- Karnofsky Performance Status score $\geq 70\%$
- Patient understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the Food and Drug Administration label (see Policy Guidelines).

Tumor treating fields therapy is considered **investigational** in all other conditions, including but not limited to the following situations:

- As an adjunct to standard medical therapy (eg, bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
- For brain metastases
- For cancer in areas other than the brain.

POLICY GUIDELINES

Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth $>25\%$ compared with the smallest tumor area measured in the patient during the trial or appearance of 1 or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).

The Food and Drug Administration label includes the following notices:

- Patients should use Optune for at least 18 hours a day to get the best response to treatment
- Patients should finish at least 4 full weeks of therapy to get the best response to treatment. Stopping treatment before 4 weeks lowers the chances of a response to treatment.

There are no specific codes for the initial application of this system or instruction on use. The patient reapplies the transducer arrays at home after the initial instruction.

There are HCPCS codes for the system and the transducer arrays:

E0766 Electrical stimulation device, used for cancer treatment, includes all accessories, any type

A4555 Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only.

BENEFIT APPLICATION

BlueCard/National Account Issues

State or federal mandates (eg, Federal Employee Program) may dictate that certain U.S. Food and Drug Administration-approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only on the basis of their medical necessity.

BACKGROUND

Glioblastoma Multiforme

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.¹ GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (eg, bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors.¹ The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to 1 year, and the 5-year survival rate was around 5%.²

Clinical Context and Therapy Purpose

The purpose of alternating electrical field therapy, more commonly known as tumor treating fields (TTF) therapy, is to provide a treatment option that is better than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

Treatment of Newly Diagnosed GBM

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these 2 therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles. Response and overall survival rates with temozolomide are higher in patients who have O⁶-methylguanine-DNA methyltransferase (*MGMT*) gene promoter methylation (see 2.04.113 on *MGMT* promoter methylation for malignant gliomas).

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice (see the Supplemental Information section).³ For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur essentially all patients.

Treatment of Recurrent GBM

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivascular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (eg, lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at 6 months is less than 20%.⁴ There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

The questions addressed in this evidence review are:

- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

Interventions

TTF therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields.⁴⁻⁶ TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. TTF therapy is proposed to inhibit tumor growth by 2 mechanisms:

the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase.^{5,6} Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune (formerly NovoTTF-100A System) is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

Comparators

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

The following practices are currently being used to make decisions about recurrent GBM: medical therapy.

TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds 3 to 5 months.⁴

Outcomes

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

Timing

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.

Setting

The setting is outpatient care by an oncologist or neuro-oncologist.

Regulatory Status

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process.⁷ The FDA-approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, FDA approved Novocure's request for a product name change from NovoTTF-110A System to Optune®.⁸

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.⁹ The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

FDA product code: NZK.

RATIONALE

This evidence review was created in August 2013 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through April 5, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

For this review, 3 indications are evaluated: (1) tumor treating fields (TTF) as an adjunct to maintenance chemotherapy in newly diagnosed patients following initial treatment with surgery, radiotherapy and chemotherapy and (2) TTF as an adjunct or (3) alternative to medical therapy (eg, bevacizumab, chemotherapy) in progressive or recurrent glioblastoma multiforme (GBM).

Study Selection

The PICOTS was used to select relevant studies.

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Within each category of study design, studies with larger sample size studies and longer duration were sought.

TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM

Randomized Controlled Trials

Stupp et al (2017) published results of the EF-14 multicenter, open-label phase 3 RCT that evaluated maintenance therapy with TTF for newly diagnosed GBM.¹⁰ The trial included 695 patients from 83 sites who had supratentorial GBM and had completed standard treatment consisting of biopsy or surgical resection followed by radiotherapy and chemotherapy (see Table 1). A Karnofsky Performance Status (KPS) score of 70 or higher was an additional inclusion criterion to ensure independence in activities of daily living, and patients with rapidly progressing GBM following radiochemotherapy were excluded from the trial. Patients were randomized in a 2:1 fashion to TTF plus maintenance temozolomide or maintenance temozolomide alone.

All patients were seen monthly for follow-up. Quality of life (QOL) was assessed every 3 months, and magnetic resonance imaging (MRI) was performed every 2 months until tumor progression. Tumor progression on MRI was adjudicated by a central review committee blinded to treatment group. The primary outcome was progression-free survival (PFS), and the secondary outcome was overall survival (OS). The analysis was by intention-to-treat, including 26 patients from the control arm who crossed over to TTF following the planned interim analysis.

In 2014, an independent data and safety monitoring board concluded from the planned interim analysis that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended trial termination. The Food and Drug Administration approved the trial termination, and the trial was closed to recruitment with 695 of the planned 700 participants randomized. Control arm participants were allowed to cross over to the experimental treatment at this time. The interim analysis, which the Food and Drug Administration considered for the 2015 expanded approval of Optune, was published by Stupp et al (2015).¹¹ At the time of the interim analysis, data were available for 210 patients randomized to TTF plus temozolomide and 105 patients to temozolomide alone. Follow-up of the remainder of the 695 enrolled patients continued after enrollment was closed.

Table 1. Key Randomized Controlled Trial Characteristics for Newly Diagnosed Glioblastoma

| Study; Trial | Countries | Sites | Dates | Participants | Interventions | |
|------------------------------------------|---------------------------------|-------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|----------------------------------------------------------------------|
| | | | | | Active | Comparator |
| Stupp et al (2017) ¹⁰ ; EF-14 | U.S., E.U., South Korea, Israel | 83 | 2009-2016 | <ul style="list-style-type: none"> • 695 newly diagnosed with GBM and treated by radiochemotherapy • KPS score ≥ 70 | TTF >18 h/d plus maintenance temozolomide (n=466) | Maintenance temozolomide alone (5 d every 28 d for 6 cycles) (n=229) |

GBM: glioblastoma multiforme; h/d: hours per day; KPS: Karnofsky Performance Status; TTF: tumor treatment fields.

Results of the final analysis of the EF-14 trial were similar to the interim analysis and are shown in Table 2. Both PFS and OS improved with the addition of TTF therapy to standard maintenance chemotherapy (ie, temozolomide). PFS increased by 2.7 mo ($p < 0.001$) and OS increased by 4.9 mo ($p < 0.001$) in the TTF group. The time to a decrease in mental function was 2.5 months longer with TTF therapy ($p < 0.01$).

There was a similar percentage of dropouts at the final analysis—with 49 (11%) patients in the TTF group and 27 (12%) patients in the temozolomide alone group. More treatment cycles with temozolomide were administered in the TTF group (median, 6 for TTF group vs 5 for controls), a finding that is consistent with the longer PFS. Rates of adverse events were similar between the groups, including rates of seizures. In secondary analysis of patients who had not progressed, there

was no reduction in health-related quality of life with TTF compared with temozolomide alone aside from "itchy skin".¹² Interpretation of this result is limited by the low percentage of patients who completed the health-related quality of life assessments at follow-up (65.8% of the 655 patients alive at 3 months and 41.7% of the 473 patients alive at 12 months). A mixed-model analysis, which accounts for missing data, confirmed the results of the mean change from baseline analysis.

Table 2. Key Randomized Controlled Trial Results for Newly Diagnosed Glioblastoma

| Study | Final N (%) | Median PFS (95% CI), mo | Median OS (95% CI), mo | Systemic Adverse Events, n (%) | Seizures, n (%) | Time to 6-Point Decline in MMSE Score (95% CI), mo |
|----------------------------------|-------------|-------------------------|------------------------|--------------------------------|-----------------|----------------------------------------------------|
| Stupp et al (2017) ¹⁰ | | | | | | |
| TTF + temozolomide | 417 (89) | 6.7 (6.1 to 8.1) | 20.9 (19.3 to 22.7) | 218 (48) | 26 (6) | 16.7 (14.7 to 19.0) |
| Temozolomide alone | 202 (88) | 4.0 (3.8 to 4.4) | 16.0 (14.0 to 18.4) | 94 (44) | 13 (6) | 14.2 (12.7 to 17.0) |
| HR (95% CI) | | 0.63 (0.52 to 0.76) | 0.63 (0.53 to 0.76) | | | 0.79 (0.66 to 0.95) |
| P value | | <0.001 | <0.001 | 0.58 | | 0.01 |

CI: confidence interval; HR: hazard ratio; MMSE: Mini-Mental State Examination; OS: overall survival; PFS: progression-free survival; TTF: tumor treatment fields.

Tables 3 and 4 display notable gaps identified in this trial, the major limitation is the lack of patient blinding to treatment assignment. However, PFS was assessed by investigators who were blinded to treatment and placebo effects on OS were expected to be minimal. Investigators considered it practically unfeasible (due to the heat and current of the TTF therapy) and ethically unacceptable to submit the control patients to repeated shaving of the head and continuous wear of a sham device over many months.

Table 3. Relevance Gaps

| Study; Trial | Population ^a | Intervention ^b | Comparator ^c | Outcomes ^d | Follow-Up ^e |
|------------------------------------------|-------------------------|---------------------------|----------------------------------------------------------------------------------|-----------------------|------------------------|
| Stupp et al (2017) ¹⁰ ; EF-14 | | | 3. Possible differences in post-progression treatment affecting overall survival | | |

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 4. Study Design and Conduct Gaps

| Study; Trial | Allocation ^a | Blinding ^b | Selective Reporting ^c | Data Completeness ^d | Power ^e | Statistical ^f |
|------------------------------------------|-------------------------|------------------------------------------------------------|----------------------------------|--------------------------------|--------------------|--------------------------|
| Stupp et al (2017) ¹⁰ ; EF-14 | | 1. No sham control and not blinded to treatment assignment | | | | |

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM

The final analysis of the EF-14 trial, which included 695 patients from 83 sites, found a statistically and clinically significant increase of 2.7 months in PFS and an increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. There was no sham control, and patients were not blinded to treatment assignment, but PFS was assessed by blinded evaluators, and placebo effects on the

objective measure of OS were likely to be minimal. There was no evidence of a negative impact of TTF therapy on health-related quality of life, except for itchy skin from the transducers.

TTF Therapy as an Adjunct or Alternative to Medical Therapy for Progressive or Recurrent GBM

Randomized Controlled Trials

The 2011 Food and Drug Administration approval of the NovoTTF-100A System (now called Optune) was based on a phase 3 multinational RCT (EF-11), results of which were published by Stupp et al (2012).⁴ This trial compared TTF therapy alone with physician's choice medical therapy in 237 adults who had relapsed or progressive glioblastoma (see Table 5). Patients had failed conventional treatment with radiotherapy, chemotherapy, and/or surgery, and more than 80% of participants had failed 2 or more prior chemotherapy regimens. In this trial, the term chemotherapy also applied to targeted agents such as bevacizumab. Patient characteristics and performance of additional post-recurrence debulking surgery were similar in the 2 groups.

Table 5. Summary of Key Randomized Controlled Trial Characteristics for Progressive or Recurrent Glioblastoma

| Study; Trial | Countries | Sites | Dates | Participants | Interventions |
|-----------------------------------------|--------------------|-------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| | | | | | Active Comparator |
| Stupp et al (2012) ⁴ ; EF-11 | U.S., E.U., Israel | 28 | 1987-2013 | <ul style="list-style-type: none"> 237 adults with relapsed or progressive supratentorial glioblastoma KPS score $\geq 70\%$ | 120 patients treated with TTF alone, 93 (78%) completed 1 cycle 117 patients treated with physician's choice of medical therapy ^a |

EU: European Union; KPS: Karnofsky Performance Status; TTF: tumor treating fields.

^a Medical therapy included bevacizumab, irinotecan, nitrosoureas, platinum-based chemotherapy (ie, carboplatin); temozolomide; or a combination of procarbazine, chloroethyl ether, and vincristine.

Participants were followed monthly, including laboratory tests. MRI images were evaluated at 2, 4, and 6 months from initiation of treatment, with subsequent MRIs performed according to local practice until disease progression. QOL questionnaires were completed every 3 months. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess mortality rates. The primary end point was OS. Secondary end points included PFS, the percentage of patients with PFS at 6 months, time to progression, 1-year survival rate, QOL, and radiologic response. All end points were evaluated using intention-to-treat analysis.

The trial did not reach its primary end point of improved survival compared with active medical therapy (see Table 6). With a median follow-up of 39 months, 93% of patients had died. There was not a statistically significant difference in survival rates at 1, 2, and 3 years between groups. Patients in the TTF group did not, however, suffer the typical systemic side effects of chemotherapy. The most common adverse event in the TTF group was grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids and did not require treatment breaks. Control participants experienced grade 2, 3, or 4 events by organ system related to the pharmacologic activity of chemotherapy agents used. Hematologic events of grade 2 or greater were observed in 17% of chemotherapy patients compared with 3% of TTF patients. Gastrointestinal disorders of grade 2 or greater were identified in 17% of chemotherapy patients compared with 4% of TTF patients. Severe (grades 3-4) hematologic and gastrointestinal toxicity was observed in 7% of chemotherapy controls compared with 1% of the TTF group.

Longitudinal QOL data, available in 63 (27%) participants, showed no meaningful differences between groups for the domains of global health and social functioning. However, cognitive and emotional functioning domains favored TTF therapy. Symptom scale analysis was by treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration.

The trial had a number of limitations (see Tables 7 and 8), that included lack of blinding and high loss to follow-up. Discontinuation of TTF therapy occurred in 22% of patients due to noncompliance or inability to handle the device, usually within the first few days. In the control group, 21 (18%) patients did not return to the treatment site, and details on disease progression and toxicity were not available. Longitudinal QOL could be analyzed only for 27% of patients who remained on study therapy for 3 months. The trial was designed as a superiority trial and did not provide adequate evidence of noninferiority.

Table 6. Summary of Key Randomized Controlled Trial Results for Recurrent or Progressive Glioblastoma

| Study; Trial | LTFU, n (%) | Median OS, mo | Progression-Free Survival | | Overall Survival (95% CI), % | | |
|---------------------------------------------|-------------|----------------------------|----------------------------|------------------------------|------------------------------|-------------|------------|
| | | | Median, mo | Rate at 6 Months (95% CI), % | 1 Year | 2 Years | 3 Years |
| Stupp et al (2012) ⁴ ; EF-11 TTF | 23 (22) | 6.6 | 2.2 | 21.4 (13.5 to 29.3) | 20 | 8 (4 to 13) | 4 (1 to 8) |
| PCC HR (95% CI) | 12 (18) | 6.0 0.86 (0.66 to 1.12) | 2.1 0.81 (0.60 to 1.09) | 15.1 (7.8 to 22.3) | 20 | 5 (3 to 10) | 1 (0 to 3) |

P value 0.27 0.16 0.13

CI: confidence interval; HR: hazard ratio; LTFU: loss to follow-up; PCC: physician's choice chemotherapy; TTF: tumor treating fields.

Table 7. Relevance Gaps

| Study | Population ^a | Intervention ^b | Comparator ^c | Outcomes ^d | Follow-Up ^e |
|-----------------------------------------|-------------------------|---------------------------|------------------------------------|-----------------------|------------------------|
| Stupp et al (2012) ⁴ ; EF-11 | | | 2. Physician's choice chemotherapy | | |

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Gaps

| Study; Trial | Allocation ^a | Blinding ^b | Selective Reporting ^d | Data Completeness ^e | Power ^d | Statistical ^f |
|-----------------------------------------|-------------------------|----------------------------------------|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-------------------------------------------|
| Stupp et al (2012) ⁴ ; EF-11 | | 1. Not blinded to treatment assignment | | 1. 78% of TTF group completed only 1 cycle of therapy, 18% of control group lost to follow-up 1. Longitudinal QOL data were available for 27% of patients | | 1. Not designed as a noninferiority trial |

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

QOL: quality of life.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Nonrandomized Comparative Studies

Kesari et al (2017) conducted a post hoc analysis of the EF-14 trial (see Stupp et al [2017] above) to evaluate the efficacy of TTF in patients who had the first recurrence.¹³ Some patients in the temozolomide alone group crossed over to receive TTF plus chemotherapy after the first recurrence, resulting in 144 patients who received TTF fields plus chemotherapy and 30 patients who received chemotherapy alone for recurrent GBM (see Table 9). Patient characteristics and second-line treatments were well-balanced between the groups, with bevacizumab the most common second-line therapy. The median OS in patients treated with systemic therapy alone was 9.2 months (see Table 10). In comparison, the group of patients who received TTF therapy in addition to systemic therapy had a median OS of 11.8 months (p=0.043).

A registry study published Mrugala et al (2014) assessed OS data from patients who received NovoTTF therapy in a real-world, clinical practice setting (see Table 9).¹⁴ Concurrent treatment was not captured in the registry, and it is possible that some patients received combination therapy. Median OS in the PRiDe clinical practice dataset (9.6 mo) was reported as superior to that attained in the EF-11 pivotal trial (6.6 mo, p<0.001) (see Table 10). More patients in the PRiDe registry were treated for first recurrence (33% vs 9%), and more had received bevacizumab as prior therapy (55% vs 19%). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

Table 9. Characteristics of Key Nonrandomized Trial Results

| Study | Study Type | Country | Dates | Participants | TTF | Controls | FU |
|------------------------------------|-------------------------|---------------------------------|-----------|-------------------------------------------------------|----------------------------------------------------------------------------------------------|---------------------------------------------------------|---------|
| Kesari et al (2017) ¹³ | EF-14 post hoc analysis | U.S., E.U., South Korea, Israel | 2009-2016 | 204 patients with first recurrence in the EF-14 trial | 144 patients treated with TTF plus second-line chemotherapy Patient Registry Dataset (PRiDe) | 60 patients treated with second-line chemotherapy EF-11 | 12.6 mo |
| Mrugala et al (2014) ¹⁴ | Registry | U.S. (91 centers) | 2011-2013 | 457 patients with recurrent GBM | | | |

FU: follow-up; GBM: glioblastoma; TTF: tumor treating fields.

Table 10. Summary of Key Nonrandomized Trial Results

| Study | Median OS, mo | Median OS With Bevacizumab, mo |
|-------|---------------|--------------------------------|
|-------|---------------|--------------------------------|

Kesari et al (2017)¹³, EF-14

| | | |
|-----------------------|---------------------|---------------------|
| TTF plus chemotherapy | 11.8 | 11.8 |
| Chemotherapy alone | 9.2 | 9.0 |
| Hazard ratio (95% CI) | 0.70 (0.48 to 1.00) | 0.61 (0.37 to 0.99) |
| P value | 0.049 | 0.043 |

1-Year OS, %**2-Year OS, %****Mrugala et al (2014)¹⁴**

| | |
|-----------------------|---------------------|
| PRIDe Registry | 9.6 |
| EF-11 | 6.6 |
| Hazard ratio (95% CI) | 0.66 (0.05 to 0.86) |

44
2030
9

P value <0.001

CI: confidence interval; OS: overall survival, TTF: tumor treating fields.

Post hoc analyses of the EF-11 pivotal trial have been reported. Wong et al (2014) published a subgroup analysis to determine characteristics of responders and nonresponders in the active treatment and active treatment control.¹⁵ They found that responders had a lower grade of histology and lower daily dexamethasone use than nonresponders. A second post hoc analysis by Kanner et al (2014) of the EF-11 pivotal trial data was performed to evaluate OS among patients who finished at least 1 complete course of TTF or chemotherapy.¹⁶ The investigators reported that median OS was 7.7 months in the TTF group compared with 5.9 months in the chemotherapy group (p=0.009). These post hoc analyses are considered to be hypothesis-generating.

Section Summary: TTF Therapy as an Adjunct or Alternative to Chemotherapy for Progressive or Recurrent GBM

The single RCT for TTF as an alternative to chemotherapy reported that outcomes following TTF therapy were similar to outcomes following standard chemotherapy. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. The noninferiority of TTF compared with chemotherapy might be considered a sufficient health benefit, if TTF reduced treatment toxicity. However, because the trial was not designed as a noninferiority trial no inferences of noninferiority compared with chemotherapy can be made. Physician's choice therapy during the trial was heterogenous, although analysis indicated that survival was not affected by choice of chemotherapy. More patients in the TTF group than in the control group did not complete the treatment course. The number of patients who contributed QOL data was approximately one-quarter of total enrollment, and the self-reported QOL indicators might have been subject to bias due to the lack of blinding.

A nonrandomized post hoc evaluation of the EF-14 trial suggests that TTF may improve survival when combined with chemotherapy for recurrent GBM. This analysis should be considered hypothesis-generating, and further study in high-quality RCTs is needed.

Summary of Evidence

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes an RCT. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION**Clinical Input From Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 3 physician specialty societies (one of which provided 6 responses and 2 of which provided 1 response each) and 1 academic medical center (total of 9 individual responses) while this policy was under review in 2016. There was majority support, but not consensus, for the use of tumor treatment fields therapy as an adjunct to maintenance treatment following initial therapy for glioblastoma multiforme. There was mixed support for the use of tumor treatment fields as an alternative to chemotherapy in advanced or recurrent glioblastoma multiforme.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2018) include recommendations for the treatment of glioblastoma (see Table 11).³ For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate O⁶-methylguanine-DNA methyltransferase promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric field therapy is a category 1 recommendation. Alternating electric currents therapy is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a category 2B recommendation.

Table 11. Guidelines for Adjuvant Treatment of Glioblastoma, by Age and Performance Status

| Age, y | KPS Score, % | Treatment Options | Category |
|--------|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| ≤70 | ≥60 | <ul style="list-style-type: none"> Standard RT plus concurrent and adjuvant temozolomide plus TTF Standard RT plus concurrent and adjuvant temozolomide | 1 |
| ≤70 | <60 | <ul style="list-style-type: none"> Hypofractionated RT with/without concurrent or adjuvant temozolomide Temozolomide Palliative/best supportive care | 2A |
| >70 | ≥60 | <ul style="list-style-type: none"> Hypofractionated RT plus concurrent and adjuvant temozolomide Standard RT plus concurrent and adjuvant temozolomide plus TTF Temozolomide alone | 1 |
| >70 | <60 | <ul style="list-style-type: none"> Hypofractionated brain RT alone Hypofractionated brain RT alone Temozolomide alone Palliative/best supportive care | 2A |

KPS: Karnofsky Performance Status; RT: radiotherapy; TTF: tumor treating fields.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 12. Of particular note are the phase 3 trials evaluating TTF therapy in non-small-cell lung cancer and pancreatic cancer. TTF therapy is an active area of research for mechanisms underlying its effects on cancer cells.

Table 12. Summary of Key Trials

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Ongoing | | | |
| NCT01971281 ^a | A Phase II Study of TTFields (150 kHz) Concomitant With Gemcitabine and TTFields Concomitant With Gemcitabine Plus Nab-paclitaxel for Front-line Therapy of Advanced Pancreatic Adenocarcinoma | 40 | Dec 2017 (ongoing) |
| NCT01894061 ^a | A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma | 40 | Dec 2018 |
| NCT02663271 ^a | A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the Combination of TTFields and Pulsed Bevacizumab Treatment in Patients With Bevacizumab-refractory Recurrent Glioblastoma | 18 | Mar 2019 |
| NCT02831959 ^a | Pivotal, Open-label, Randomized Study of Radiosurgery With or Without Tumor Treating Fields (TTFields) (150kHz) for 1-10 Brain Metastases From Non-small Cell Lung Cancer (NSCLC) (METIS) | 270 | Jul 2019 |
| NCT02973789 ^a | LUNAR: Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields) Concurrent With Standard of Care Therapies for Treatment of Stage 4 Non-small Cell Lung Cancer (NSCLC) Following Platinum Failure | 534 | Dec 2021 |
| NCT02743078 ^a | Phase II Trial Of Optune® Plus Bevacizumab In Bevacizumab-Refractory Recurrent Glioblastoma | 85 | Aug 2022 |

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------------|
| NCT03377491 ^a | EF-27 Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields, 150kHz) Concomitant With Gemcitabine and Nab-paclitaxel for Front-line Treatment of Locally-advanced Pancreatic Adenocarcinoma (PANOVA-3) | 556 | Dec 2022 |

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

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CODES

| Codes | Number | Description |
|------------------|-------------|---------------------------------------------------------------------------------------------------------------|
| CPT | | No specific code – See Policy Guidelines |
| | 191.0-191.9 | Malignant neoplasm of brain code range |
| HCPCS | A4555 | Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only |
| | E0766 | Electrical stimulation device, used for cancer treatment, includes all accessories, any type |
| ICD-10-CM | | Investigational for all relevant diagnoses |
| | C71.0-C71.9 | Malignant neoplasm of brain code range |
| ICD-10-PCS | | Not applicable. Policy is only for outpatient services. ICD-10-PCS codes are only used for inpatient services |
| Type of Service | | |
| Place of Service | | |

Posted on: 08/17/2018

TUMOR-TREATMENT FIELDS THERAPY FOR GLIOBLASTOMA (REQUIRES PREAUTHORIZATION) VIII.9

DESCRIPTION

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults. They comprise approximately 15% of all brain and central nervous system tumors, and more than 50% of all tumors that arise from glial cells. The peak incidence for GBM occurs between the ages of 45 and 70 years. GBMs are grade IV astrocytoma and are often resistant to standard chemotherapy. According to the National Comprehensive Cancer Network, GBM is the "deadliest brain tumor with only a third of patients surviving for 1 year and less than 5% living beyond 5 years.

Alternating electric fields, generated by insulated electrodes, have been reported to exhibit inhibitory effect on the growth rate of variety of human and rodent tumor cell lines as well as malignant tumors in animals. This non-thermal effect selectively affects dividing cells while quiescent cells are left intact.

DATES

Original Effective

07-20-2016

Last Review

11-08-2017

Next Review

11-30-2018

POLICY

I. Tumor treatment fields therapy may be considered **medically necessary** as combination therapy for glioblastoma when **ALL** of the following are met:

- A. the member is 18 years of age or older **AND**
- B. the member is newly diagnosed with supratentorial, histologically confirmed glioblastoma **AND**
- C. will be used with temozolomide (TMZ) following initial treatment with surgery, chemotherapy or radiation.

18/17/2018 BCBSNE Medical Policy
Tumor treatment fields therapy may be considered **medically necessary** as monotherapy for glioblastoma when **ALL** of the following are met:

- A. the member is 18 years of age or older **AND**
- B. the member has recurrence of supratentorial, histologically confirmed glioblastoma **AND**
- C. following initial treatment with chemotherapy or radiation

III. Tumor treatment fields therapy for all other indications is considered **investigational** as the clinical effectiveness has not been established.

BACKGROUND

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults. They comprise approximately 15% of all brain and central nervous system tumors and more than 50% of all tumors that arise from glial cells.¹ The peak incidence for GBM occurs between the ages of 45 and 70 years. GBMs are grade IV astrocytomas, the most deadly type of glial cell tumor, and are often resistant to standard chemotherapy.¹ According to the National Comprehensive Cancer Network, GBM is the "deadliest brain tumor with only a third of patients surviving for 1 year and less than 5% living beyond 5 years."²

The primary treatment for GBM is debulking surgery to remove as much of the tumor as possible. At that time, some patients may undergo implantation of the tumor cavity with a carmustine (bischloroethylnitrosourea [BCNU]) impregnated wafer.² Depending on the patient's physical condition, adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of the 2 are sometimes given. After adjuvant therapy, some patients may undergo maintenance therapy with temozolomide.

No standard treatment exists for recurrent GBM. In patients with disease that recurs after these initial therapies, additional debulking surgery may be used if recurrence is localized. Other treatment options for recurrent disease include various forms of systemic medications such as bevacizumab, bevacizumab plus chemotherapy (eg, irinotecan, BCNU/chloroethylnitrosourea [CCNU], temozolomide), temozolomide, nitrosourea, PCV (procarbazine, CCNU, vincristine), cyclophosphamide, and platinum-based agents.² External beam radiotherapy (EBRT) also may be used to treat recurrent GBM. Response rates in recurrent disease are less than 10%, and progression-free survival rates at 6 months are less than 20%.^{2,3}

TTF therapy is a new, noninvasive technology that is intended to treat GBM on an outpatient basis using electrical fields.³⁻⁵ TTF therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively inhibit tumor growth and reduce tumor angiogenesis. TTF are proposed to inhibit rapidly dividing tumor cells by 2 mechanisms, arrest of cell proliferation and destruction of cells while undergoing division.^{4,5}

The NovoTTF-100A™ System (Novocure, Haifa, Israel) has received FDA marketing approval to deliver TTF therapy. TTF therapy via the NovoTTF-100A™ System is delivered by a battery-powered, portable device that generates the fields via disposable electrodes that are noninvasively attached to the patient's shaved scalp over the site of the

tumor.^{3,4} The device is used by the patient at home on a continuous basis (20-24 h/d) for the duration of treatment, which can last for several months. Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living.^{3,4}

RATIONALE

This evidence review was created in August 2013 and updated periodically through literature reviews, most recently through July 8, 2015. No new studies were identified that would change the conclusions of the evidence review. Following is a summary of the key literature.

Randomized Controlled Trials

The U.S. Food and Drug Administration (FDA) approval of the NovoTTF-100A system was based on a phase 3, multinational prospective randomized controlled trial (RCT) (EF11) which was published in 2012 by Stupp et al. The Stupp study, which was sponsored and funded by the manufacturer of the device (Novocure), compared tumor-treatment fields (TTF) therapy (delivered by the NovoTTF-100A System) with the best standard of care chemotherapy (active control).³ Twenty-eight clinical centers (across 7 countries) enrolled 237 adult participants with relapsed or progressive glioblastoma multiforme (GBM), despite conventional radiotherapy. Other prior treatments may have included surgery and/or chemotherapy. Patient characteristics were balanced in both groups, with median age of 54 years and median Karnofsky Performance Status score of 80%. More than 80% of participants had failed 2 or more prior chemotherapy regimens (\geq second recurrence), and 20% had failed bevacizumab before study enrollment.

Two hundred thirty-seven patients were randomized in a 1:1 ratio to receive TTF therapy only (n=120) or active control (n=117). The choice of chemotherapy regimens varied, reflecting local practice at each of the participating clinical centers. Chemotherapy agents considered as active control during the trial included platinum-based chemotherapy (ie, carboplatin); nitrosoureas; procarbazine; combination of procarbazine, lomustine and vincristine (PCV); temozolomide; and bevacizumab. For patients assigned to the TTF group, uninterrupted treatment was recommended, although patients were allowed to take treatment breaks of up to 1 hour, twice per day, for personal needs (eg, shower). In addition, patients assigned to the TTF group were allowed to take 2 to 3 days off treatment at the end of each of 4-week period (which is the minimal required treatment duration for TTF therapy to reverse tumor growth). A period of 28 days of treatment with TTF was considered 1 full treatment course.

The primary study end point in this RCT was overall survival (OS).³ Secondary end points included progression-free survival (PFS) at 6 months, TTP, 1-year survival rate, quality of life (QOL), and radiologic response. Participants were seen in clinic monthly, and magnetic resonance imaging (MRI) was performed after 2, 4, and 6 months from initiation of treatment, with subsequent MRI done according to local practice until disease progression. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess participant mortality rates.

Ninety-seven percent (116) of 120 participants in the TTF group started treatment and 93 participants (78%) completed 1 cycle (4 weeks) of therapy. Discontinuation of TTF therapy occurred in 27 participants (22%) due to noncompliance or the inability to handle the device.³ For each TTF treatment month, the median compliance was 86% (range, 41%-98%), which equaled a mean use of 20.6 hours per day. In the active control group, 113 (97%)

of the 117 assigned participants received chemotherapy and all except 1 individual completed a full treatment course. Twenty-one participants (18%) in the active control group did not return to the treating site and details on disease progression and toxicity were not available.

This RCT did not reach its primary end point of improved survival compared with active chemotherapy. With a median follow-up of 39 months, 220 participants (93%) had died. Median survival was 6.6 months in the TTF group compared with 6.0 months in the active control group (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.66 to 1.12; $p=0.27$). For both groups, 1-year survival was 20%. The survival rates for 2- and 3-year survival were 8% and 4%, respectively, for the TTF group versus 5% and 1%, respectively, for the active control group. PFS rate at 6 months was 21.4% in the TTF group, compared with 15.1% in the active control group ($p=0.13$). Objective radiologic responses (partial and complete response) were noted in 14 participants in the TTF group and 7 in the active control group, with a calculated response rate of 14.0% (95% CI, 7.9% to 22.4%) versus 9.6% (95% CI, 3.9% to 18.8%), respectively. Sixteen percent of the TTF participants had grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids. Active control participants experienced grade 2 to 4 events by organ system related to the pharmacologic activity of chemotherapy agents used; severe (grades 3 and 4) toxicity was observed in 3% of participants.

Longitudinal QOL data were available in 63 participants (27%). There were no meaningful differences observed between the groups in the domains of global health and social functioning. However, cognitive, emotional, and role functioning favored TTF therapy, whereas physical functioning favored chemotherapy. Symptom scale analysis was in accordance to treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the TTF group.

In summary, this RCT failed to demonstrate the primary end point of improved survival with TTF therapy in comparison with chemotherapy.^{3,9} Limitations of the trial included a somewhat heterogeneous patient population, with participants included after progression of 1 or several lines of chemotherapy, as well as the use of different chemotherapy regimens in the control group. Another limitation is the absence of a placebo/supportive care arm. In the setting of advanced disease, the supportive care arm would have been useful to gauge the safety and efficacy of treatment for both groups of patients. Treatments used in the active control arm (best standard of care chemotherapy) in the recurrent disease setting have previously demonstrated limited efficacy, thus limiting the ability to determine the true treatment effect of TTF. Data from a trial of TTF versus placebo, or TTF plus standard chemotherapy versus standard chemotherapy alone would therefore provide a better assessment of treatment efficacy. The latter study design is being used in an ongoing trial of TTF therapy in the treatment of patients with newly diagnosed GBM (see Ongoing and Unpublished Clinical Trials section).

A further limitation was high dropout rates in both groups. For example, over 20% of participants in the active control group were lost at follow-up, and this degree of the number of dropouts may have underestimated the toxicity evaluation in this group. Similarly, over 20% of participants in the TTF arm discontinued treatment within a few days due to noncompliance or inability to handle the device. This implies that compliance might be an issue with TTF, because it requires the patient to continuously wear transducers on the shaved head. Finally, the number of patients who completed the QOL data was approximately one quarter of total enrollment, and the self-reported QOL indicators may have been subject to bias due to the lack of blinding.^{3,6}

Wong et al published a subgroup analysis of the previously described RCT to determine characteristics of responders and nonresponders in the treatment and active control groups.¹⁰ Tumor response was assessed by the Macdonald criteria. More patients in the TTF arm were considered responders (14/120 vs 7/117 in the chemotherapy arm.) Median response time was longer for those in the TTF arm than the chemotherapy arm (7.3 months vs 5.6 months, $p<0.001$), and there was a strong correlation (Pearson's r) between response and OS in the

TTF arm ($p < 0.001$) but not in the chemotherapy arm ($p = 0.29$). Compared with the chemotherapy arm, a higher proportion of responders in the TTF arm had a prior lowgrade histology (36% vs 0%). These differences in treatment responder groups suggest that TTF therapy may differentially benefit certain types of GBM; however, the small numbers of responders in both groups limits generalizations that can be drawn from this analysis.

A second post hoc analysis of the TTF EF-11 pivotal trial data was performed to evaluate OS rates among patients who completed at least 1 complete course of TTF or chemotherapy.¹¹ These investigators analyzed survival in what they referred to as a “modified ITT [intention-to-treat]” subgroup comprising 93 of 120 (78%) of the original TTF allocated group, versus 117 of 117 (100%) of the original chemotherapy allocated group. This exercise revealed median OS of 7.7 months in the TTF modified ITT (mITT) group compared with 5.9 months in the chemotherapy group (HR=0.69; 95% CI, 0.52 to 0.91; $p = 0.009$). They also showed a trend relationship between proportion of patients with higher TTF compliance and median OS rates ($p = 0.039$). The investigators suggest that TTF provides an OS benefit if used as intended in the FDA-approved label when compared with best chemotherapy. This post hoc analysis is limited as it was not prespecified in the study, includes only 78% of the original TTF allocated patients, and fails to control for noncompliance due to faster clinical deterioration of TTF recipients leading to treatment cessation.

Noncomparative Studies

A study published in late 2014 included OS data from 457 patients included in the Patient Registry Dataset (PRiDe), a postmarketing registry of all recurrent GBM patients who received NovoTTF therapy in a real-world, clinical practice setting in 91 centers in the United States between October 2011 and November 2013.¹² The median OS rate in the PRiDe clinical practice dataset was reported as significantly superior to that attained in the TTF EF-11 pivotal trial (9.6 months vs 6.6 months; HR=0.66, 95% CI, 0.05 to 0.86; $p < 0.001$). One- and 2-year OS rates for TTF in PRiDe were significantly longer than those in the TTF group in the EF-11 trial (44% vs 20% at 1 year; 30% vs 9% at 2 years, respectively). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

The use of TTF and the corresponding effects on living tissue have been evaluated in uncontrolled studies in a number of clinical settings.¹³⁻¹⁵ Kirson et al (2007), for example, reported the findings of a case study examining the effects of TTF therapy delivered by the NovoTTF-100A System in 10 patients with recurrent GBM.¹³ Median time to progression (TTP) in these patients was 26.1 weeks, and median OS was 62.2 weeks. The authors noted that these TTP and OS values were more than double the reported medians of historical control patients. No device-related serious adverse events were seen after more than 70 months of cumulative treatment in all of the patients. The only device-related adverse event observed was a mild-to-moderate contact dermatitis beneath the field delivering electrodes. The primary limitation of this study was the use of historical controls, because the patients included may not be comparable on major clinical and prognostic features.¹³

Two small case series have been published of long-term survival (>6 years) with TTF therapy.^{16,17} Rulseh et al reported long-term (>7 year) survival in 4 of 20 patients with GBM who were treated with TTF,¹⁶ while Villano et al describe 1 patient with recurrent GBM who was tumor-free more than 6 years after treatment with TTF.¹⁷

Since the approval of the NovoTTF device, additional case reports and small case series have been reported. Elzinga and Wong reported a case of a patient who demonstrated improved tumor response to bevacizumab in a patient who also received TTF therapy.¹⁸ Another case series ($n = 3$) suggested that adjusting the size of the electric fields may improve response in cases of local tumor progression.¹⁹

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------------|
| Ongoing | | | |
| NCT00916409 ^a | A Prospective, Multi-center Trial of NovoTTF-100A Together with Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM | 700 | Jul 2016 |
| NCT01894061 ^a | A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma | 40 | Oct 2016 |
| NCT01755624 ^a | A Phase II Randomized Study of TTFeld Therapy Versus Supportive Care in Non-small Cell Lung Cancer Patients With 1-5 Brain Metastases Following Optimal Standard Local Treatment | 60 | Jul 2017 |
| NCT01756729 ^a | A Prospective, Non-randomized, Concurrent Control, Open Label, Post-approval Study of NovoTTF-100A in Recurrent GBM Patient | 486 | Jan 2018 |
| NCT01954576 | A Phase II Study of the NovoTTF-100A system, Enhanced by Genomic Analysis to Identify the Genetic Signature of Response in the Treatment of Recurrent Glioblastoma Multiforme | 30 | May 2018 |

NCT: national clinical trial. ^a Denotes industry-sponsored or cosponsored trial.

Summary of Evidence

The evidence for tumor-treatment fields therapy in patients who have recurrent glioblastoma multiforme includes a randomized controlled superiority pivotal trial using the U.S. Food and Drug Administration? approved device and a number of small observational studies. Relevant outcomes include overall survival (OS), quality of life (QOL), and treatment-related morbidity. The pivotal trial had numerous methodologic limitations and failed to demonstrate an improvement in OS or disease response. There were some differences reported in QOL, but these data were limited by a low response rate for QOL measures. In addition, the best standard chemotherapy protocols reported in the randomized controlled trial may not reflect current practice, given the increased use of bevacizumab and temozolomide for treatment of patients with recurrent glioblastoma. No data were available to address a comparison to other treatment modalities (eg, radiation, surgery, combination therapy). The evidence is insufficient to determine the effects of the technology on health outcomes.

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Tumor Treating Fields Therapy

POLICY NUMBER

A.1.01.29

DESCRIPTION

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during the course of treatment. Tumor-treatment fields therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

Glioblastoma Multiforme

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults. GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (eg, bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors. The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis at 64 years.

Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to 1 year, and the 5-year survival rate was around 5%.

Clinical Context and Therapy Purpose

The purpose of alternating electrical field therapy, more commonly known as tumor treating fields (TTF) therapy, is to provide a treatment option that is better than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

Treatment of Newly Diagnosed GBM

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bischloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these two therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles. Response and overall survival rates with temozolomide are higher in patients who have O⁶-

methylguanine-DNA methyltransferase (MGMT) gene promoter methylation (see [Analysis of MGMT Promoter Methylation in Malignant Gliomas \(https://www.bcbsms.com/medical-policy-search#/policy-detail?id=6a48bedf-61a9-4770-98a0-974038e85619\)](https://www.bcbsms.com/medical-policy-search#/policy-detail?id=6a48bedf-61a9-4770-98a0-974038e85619) medical policy).

Prognostic factors for success of therapy are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice. For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur essentially in all patients.

Treatment of Recurrent GBM

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic

medications such as the antivasculature endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (eg, lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at 6 months is less than 20%. There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

The questions addressed in this policy are:

- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature for this policy.

Patients

The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

Interventions

Tumor-treatment fields (TTF) therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields. TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. Tumor-treatment fields therapy is proposed to inhibit tumor growth by two mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase. Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune, formerly NovoTTF-100A System, is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

Comparators

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

The following practices are currently being used to make decisions about recurrent GBM: medical therapy.

TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds 3 to 5 months.

Outcomes

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

Timing

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.

Setting

The setting is outpatient care by an oncologist or neuro-oncologist.

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of tumor-treatment fields) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process. The FDA-approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM [glioblastoma multiforme], following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment, and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, FDA approved Novocure's request to change its products name from NovoTTF-110A System to Optune®.

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM. The device was granted priority review status in May 2015 because there was no legally marketed alternative device currently available for the treatment of newly diagnosed GBM that represents a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

POLICY

Tumor treating fields therapy to treat glioblastoma multiforme is considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:

- Adult patients ≥ 18 years of age
- Supratentorial tumor
- Karnofsky Performance Status score ≥ 70%
- Patient understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the Food and Drug Administration label (see Policy Guidelines).

Tumor treating fields therapy is considered **investigational** in all other conditions, including but not limited to the following situations:

- As an adjunct to standard medical therapy (eg, bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
- For brain metastases
- For cancer in areas other than the brain.

POLICY EXCEPTIONS

Federal Employee Program (FEP) may dictate that all FDA-approved devices, drugs or biologics may not be considered investigational and thus these devices may be assessed only on the basis of their medical necessity.

POLICY GUIDELINES

The coverage guidelines outlined in the Medical Policy Manual should not be used in lieu of the Member's specific benefit plan language.

Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth >25% compared with the smallest tumor area measured in the patient during the trial or appearance of one or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).

The Food and Drug Administration label includes the following notices:

- Patients should use Optune for at least 18 hours a day to get the best response to treatment
- Patients should finish at least 4 full weeks of therapy to get the best response to treatment. Stopping treatment before 4 weeks lowers the chances of a response to treatment.

Investigative is defined as the use of any treatment procedure, facility, equipment, drug, device, or supply not yet recognized as a generally accepted standard of good medical practice for the treatment of the condition being treated and; therefore, is not considered medically necessary. For the definition of Investigative, "generally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, and physician specialty society recommendations, and the views of medical practitioners practicing in relevant clinical areas and any other relevant factors. In order for equipment, devices, drugs or supplies [i.e., technologies], to be considered not investigative, the technology must have final approval from the appropriate governmental bodies, and scientific evidence must permit conclusions concerning the effect of the technology on health outcomes, and the technology must improve the net health outcome, and the technology must be as beneficial as any established alternative and the improvement must be attainable outside the testing/investigational setting.

POLICY HISTORY

04/01/2014: Approved by Medical Policy Advisory Committee.

09/30/2014: Policy reviewed; no changes.

07/23/2015: Code Reference section updated for ICD-10.

11/03/2015: Policy description updated regarding devices. Policy statement unchanged. Investigative definition updated in policy guidelines section.

01/06/2016: Code Reference section updated to add HCPCS codes A4555 and E0766 with an effective date of 01/01/2016.

05/31/2016: Policy number A.1.01.29 added.

09/22/2016: Policy description updated to add section headings. Policy statement revised for clarity; intent unchanged.

08/04/2017: Policy description updated regarding treatment for patients with glioblastoma multiforme and devices. Policy statement updated to state that tumor-treatment fields therapy to treat glioblastoma multiforme (GBM) is investigational as an alternative to standard chemotherapy for patients with progressive or recurrent GBM after initial or repeat treatment with surgery, radiotherapy, and/or chemotherapy and as an adjunct to standard maintenance therapy in patients with newly diagnosed GBM following initial treatment with surgery, radiotherapy, and/or chemotherapy.

09/15/2018: Policy title changed from "Tumor-Treatment Fields Therapy for Glioblastoma" to "Tumor Treating Fields Therapy." Policy description updated regarding treatment of newly diagnosed glioblastoma multiforme (GBM) and recurrent GBM. Added the following policy statement: Tumor treating fields therapy to treat glioblastoma multiforme is considered medically necessary as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under certain conditions. Investigational statement updated to state that tumor treating fields therapy is considered investigational in all other conditions. Policy Guidelines updated to define progression. Code Reference section updated to change codes from investigational to medically necessary and add ICD-10 diagnosis codes C71.0 - C71.9.

SOURCE(S)

<https://www.bcbsms.com/medical-policy-search#/policy-detail?id=3b7f9fd0-b5dc-42dd-a3c3-5cd36acfa49>

4/5

CODE REFERENCE

This may not be a comprehensive list of procedure codes applicable to this policy.

The code(s) listed below are **ONLY** medically necessary if the procedure is performed according to the "Policy" section of this document.

Medically Necessary Codes

| Code Number | Description |
|-------------------------|-------------------------------------------------------------------------------------------------------------|
| CPT-4 | |
| | |
| HCPCS | |
| A4555 | Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only |
| A9900 | Miscellaneous DME supply, accessory, and/or service component of another HCPCS code |
| E0766 | Electrical stimulation device used for cancer treatment, includes all accessories, any type |
| E1399 | Durable medical equipment, miscellaneous |
| ICD-10 Procedure | |
| | |
| ICD-10 Diagnosis | |
| C71.0 - C71.9 | Malignant neoplasm of brain |

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Tumor Treating Fields Therapy

POLICY NUMBER

A.1.01.29

DESCRIPTION

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during the course of treatment. Tumor-treating fields therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

Glioblastoma Multiforme

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults. GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (eg, bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors. The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis at 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to 1 year, and the 5-year survival rate was around 5%.

Clinical Context and Therapy Purpose

The purpose of alternating electrical field therapy, more commonly known as tumor treating fields (TTF) therapy, is to provide a treatment option that is better than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

Treatment of Newly Diagnosed GBM

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bischloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these two therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles. Response and overall survival rates with temozolomide are higher in patients who have O⁶-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation (see [Analysis of MGMT Promoter Methylation in Malignant Gliomas \(https://www.bcbsms.com/medical-policy-search#/policy-detail?id=6a48bedf-61a9-4770-98a0-974038e85619\)](https://www.bcbsms.com/medical-policy-search#/policy-detail?id=6a48bedf-61a9-4770-98a0-974038e85619) medical policy).

Prognostic factors for success of therapy are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice. For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur essentially in all patients.

Treatment of Recurrent GBM

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment

for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivascular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (eg, lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at 6 months is less than 20%. There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

The questions addressed in this policy are:

- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature for this policy.

Patients

The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

Interventions

Tumor-treatment fields (TTF) therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields. TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. Tumor-treatment fields therapy is proposed to inhibit tumor growth by two mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase. Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune, formerly NovoTTF-100A System, is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

Comparators

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

The following practices are currently being used to make decisions about recurrent GBM: medical therapy.

TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds 3 to 5 months.

Outcomes

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

Timing

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.

Setting

The setting is outpatient care by an oncologist or neuro-oncologist.

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of tumor-treatment fields) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process. The FDA-approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM [glioblastoma multiforme], following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment, and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, FDA approved Novocure's request to change its products name from NovoTTF-110A System to Optune®.

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM. The device was granted priority review status in May 2015 because there was no legally marketed alternative device currently available for the treatment of newly diagnosed GBM that represents a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

POLICY

Tumor treating fields therapy to treat glioblastoma multiforme is considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:

- Adult patients ≥18 years of age
- Supratentorial tumor
- Karnofsky Performance Status score ≥70%
- Patient understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the Food and Drug Administration label (see Policy Guidelines).

Tumor treating fields therapy is considered **investigational** in all other conditions, including but not limited to the following situations:

- As an adjunct to standard medical therapy (eg, bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
- For brain metastases
- For cancer in areas other than the brain.

POLICY EXCEPTIONS

Federal Employee Program (FEP) may dictate that all FDA-approved devices, drugs or biologics may not be considered investigational and thus these devices may be assessed only on the basis of their medical necessity.

POLICY GUIDELINES

The coverage guidelines outlined in the Medical Policy Manual should not be used in lieu of the Member's specific benefit plan language.

Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth >25% compared with the smallest tumor area measured in the patient during the trial or appearance of one or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).

The Food and Drug Administration label includes the following notices:

- Patients should use Optune for at least 18 hours a day to get the best response to treatment
 - Patients should finish at least 4 full weeks of therapy to get the best response to treatment.
- Stopping treatment before 4 weeks lowers the chances of a response to treatment.

Investigative is defined as the use of any treatment procedure, facility, equipment, drug, device, or supply not yet recognized as a generally accepted standard of good medical practice for the treatment of the condition being treated and; therefore, is not considered medically necessary. For the definition of Investigative, "generally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, and physician specialty society recommendations, and the views of medical practitioners practicing in relevant clinical areas and any other relevant factors. In order for equipment, devices, drugs or supplies [i.e, technologies], to be considered not investigative, the technology must have final approval from the appropriate governmental bodies, and scientific evidence must permit conclusions concerning the effect of the technology on health outcomes, and the technology must improve the net health outcome, and the technology must be as beneficial as any established alternative and the improvement must be attainable outside the testing/investigational setting.

POLICY HISTORY

04/01/2014: Approved by Medical Policy Advisory Committee.

09/30/2014: Policy reviewed; no changes.

07/23/2015: Code Reference section updated for ICD-10.

11/03/2015: Policy description updated regarding devices. Policy statement unchanged. Investigative definition updated in policy guidelines section.

01/06/2016: Code Reference section updated to add HCPCS codes A4555 and E0766 with an effective date of 01/01/2016.

05/31/2016: Policy number A.1.01.29 added.

09/22/2016: Policy description updated to add section headings. Policy statement revised for clarity; intent unchanged.

08/04/2017: Policy description updated regarding treatment for patients with glioblastoma multiforme and devices. Policy statement updated to state that tumor-treatment fields therapy to treat glioblastoma multiforme (GBM) is investigational as an alternative to standard chemotherapy for patients with progressive or recurrent GBM after initial or repeat treatment with surgery, radiotherapy, and/or chemotherapy and as an adjunct to standard maintenance therapy in patients with newly diagnosed GBM following initial treatment with surgery, radiotherapy, and/or chemotherapy.

09/15/2018: Policy title changed from "Tumor-Treatment Fields Therapy for Glioblastoma" to "Tumor Treating Fields Therapy." Policy description updated regarding treatment of newly diagnosed glioblastoma multiforme (GBM) and recurrent GBM. Added the following policy statement: Tumor treating fields therapy to treat glioblastoma multiforme is considered medically necessary as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under certain conditions. Investigational statement updated to state that tumor treating fields therapy is considered investigational in all other conditions. Policy Guidelines updated to define progression. Code Reference section updated to change codes from investigational to medically necessary and add ICD-10 diagnosis codes C71.0 - C71.9.

SOURCE(S)

Blue Cross and Blue Shield Association Policy #1.01.29

CODE REFERENCE

This may not be a comprehensive list of procedure codes applicable to this policy.

The code(s) listed below are **ONLY** medically necessary if the procedure is performed according to the "Policy" section of this document.

Medically Necessary Codes

| Code Number | Description |
|-------------------------|-------------------------------------------------------------------------------------------------------------|
| CPT-4 | |
| | |
| HCPCS | |
| A4555 | Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only |
| A9900 | Miscellaneous DME supply, accessory, and/or service component of another HCPCS code |
| E0766 | Electrical stimulation device used for cancer treatment, includes all accessories, any type |
| E1399 | Durable medical equipment, miscellaneous |
| ICD-10 Procedure | |
| | |
| ICD-10 Diagnosis | |
| C71.0 - C71.9 | Malignant neoplasm of brain |

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Kansas City

An Independent Licensee of the Blue Cross and Blue Shield Association

Tumor-Treatment Fields Therapy

Policy Number: 1.01.29

Last Review: 9/2018

Origination: 12/2013

Next Review: 12/2018

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Tumor Treating Fields Therapy when it is determined to be medically necessary because the criteria shown below are met.

Please note that this is a type of electrical stimulation that is considered a benefit exclusion in many health plan contracts.

When Policy Topic is covered

Tumor treating fields therapy to treat glioblastoma multiforme is considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:

- Adult patients ≥ 18 years of age
- Supratentorial tumor
- Karnofsky Performance Status score $\geq 70\%$
- Patient understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the Food and Drug Administration label (Considerations).

When Policy Topic is not covered

Tumor treatment fields therapy to treat glioblastoma is considered **investigational**, including but not limited to the following situations:

- As an adjunct to standard medical therapy (eg, bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
- For brain metastases
- For cancer in areas other than the brain.

Considerations

Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth $> 25\%$ compared with the smallest tumor

area measured in the patient during the trial or appearance of 1 or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).

The Food and Drug Administration label includes the following notices:

- Patients should use Optune for at least 18 hours a day to get the best response to treatment
- Patients should finish at least 4 full weeks of therapy to get the best response to treatment. Stopping treatment before 4 weeks lowers the chances of a response to treatment.

There are no specific codes for the initial application of this system or instruction on use. The patient reapplies the transducer arrays at home after the initial instruction.

There are HCPCS codes for the system and the transducer arrays:

E0766 Electrical stimulation device, used for cancer treatment, includes all accessories, any type

A4555 Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only.

Description of Procedure or Service

| Populations | Interventions | Comparators | Outcomes |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Individuals: <ul style="list-style-type: none"> • With newly diagnosed glioblastoma multiforme on maintenance therapy after initial treatment | Interventions of interest are: <ul style="list-style-type: none"> • Tumor treating fields therapy as an adjunct to standard maintenance therapy | Comparators of interest are: <ul style="list-style-type: none"> • Standard maintenance therapy alone | Relevant outcomes include: <ul style="list-style-type: none"> • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity |
| Individuals: <ul style="list-style-type: none"> • With progressive or recurrent glioblastoma multiforme | Interventions of interest are: <ul style="list-style-type: none"> • Tumor treating fields therapy as an adjunct or alternative to medical therapy | Comparators of interest are: <ul style="list-style-type: none"> • Standard medical therapy | Relevant outcomes include: <ul style="list-style-type: none"> • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity |

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes a randomized controlled trial (RCT). Relevant

outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Background

Glioblastoma Multiforme

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.¹ GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (eg, bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors.¹ The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to 1 year, and the 5-year survival rate was around 5%.²

Clinical Context and Therapy Purpose

The purpose of alternating electrical field therapy, more commonly known as tumor treating fields (TTF) therapy, is to provide a treatment option that is better

than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM

Treatment of Newly Diagnosed GBM

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these 2 therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles. Response and overall survival rates with temozolomide are higher in patients who have O⁶-methylguanine-DNA methyltransferase (*MGMT*) gene promoter methylation (see separate policy).

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice (see the Supplemental Information section).³ For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur essentially all patients.

Treatment of Recurrent GBM

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivascular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (eg, lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at 6 months is less than 20%.⁴ There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

The questions addressed in this evidence review are:

- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

Interventions

TTF therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields.⁴⁻⁶ TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. TTF therapy is proposed to inhibit tumor growth by 2 mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase.^{5,6} Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune (formerly NovoTTF-100A System) is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

Comparators

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

The following practices are currently being used to make decisions about recurrent GBM: medical therapy.

TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds 3 to 5 months.⁴

Outcomes

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

Timing

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.

Setting

The setting is outpatient care by an oncologist or neuro-oncologist.

Regulatory Status

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process.⁷ The FDA-approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, FDA approved Novocure's request for a product name change from NovoTTF-110A System to Optune®.⁸

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.⁹ The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

Rationale

This evidence review was created in August 2013 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through April 5, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

For this review, 3 indications are evaluated: (1) tumor treating fields (TTF) as an adjunct to maintenance chemotherapy in newly diagnosed patients following initial treatment with surgery, radiotherapy and chemotherapy and (2) TTF as an adjunct or (3) alternative to medical therapy (eg, bevacizumab, chemotherapy) in progressive or recurrent glioblastoma multiforme (GBM).

Study Selection

The PICOTS was used to select relevant studies.

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Within each category of study design, studies with larger sample size studies and longer duration were sought.

TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM

Randomized Controlled Trials

Stupp et al (2017) published results of the EF-14 multicenter, open-label phase 3 RCT that evaluated maintenance therapy with TTF for newly diagnosed GBM.¹⁰ The trial included 695 patients from 83 sites who had supratentorial GBM and had completed standard treatment consisting of biopsy or surgical resection followed by radiotherapy and chemotherapy (see Table 1). A Karnofsky Performance Status (KPS) score of 70 or higher was an additional inclusion criterion to ensure independence in activities of daily living, and patients with rapidly progressing GBM following radiochemotherapy were excluded from the trial. Patients were randomized in a 2:1 fashion to TTF plus maintenance temozolomide or maintenance temozolomide alone.

All patients were seen monthly for follow-up. Quality of life (QOL) was assessed every 3 months, and magnetic resonance imaging (MRI) was performed every 2 months until tumor progression. Tumor progression on MRI was adjudicated by a central review committee blinded to treatment group. The primary outcome was progression-free survival (PFS), and the secondary outcome was overall survival (OS). The analysis was by intention-to-treat, including 26 patients from the control arm who crossed over to TTF following the planned interim analysis.

In 2014, an independent data and safety monitoring board concluded from the planned interim analysis that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended trial termination. The Food and Drug Administration approved the trial termination, and the trial was closed to recruitment with 695 of the planned 700 participants randomized. Control arm participants were allowed to cross over to the experimental treatment at this time. The interim analysis, which the Food and Drug Administration considered for the 2015 expanded approval of Optune, was published by Stupp et al (2015).¹¹ At the time of the interim analysis, data were available for 210 patients randomized to TTF plus temozolomide and 105 patients to temozolomide alone. Follow-up of the remainder of the 695 enrolled patients continued after enrollment was closed.

Table 1. Key Randomized Controlled Trial Characteristics for Newly Diagnosed Glioblastoma

| Study; Trial | Countries | Sites | Dates | Participants | Interventions | |
|------------------------------------------|---------------------------------|-------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|----------------------------------------------------------------------|
| | | | | | Active | Comparator |
| Stupp et al (2017) ¹⁰ ; EF-14 | U.S., E.U., South Korea, Israel | 83 | 2009-2016 | <ul style="list-style-type: none"> 695 newly diagnosed with GBM and treated by radiochemotherapy KPS score ≥ 70 | TTF > 18 h/d plus maintenance temozolomide (n=466) | Maintenance temozolomide alone (5 d every 28 d for 6 cycles) (n=229) |

GBM: glioblastoma multiforme; h/d; hours per day; KPS: Karnofsky Performance Status; TTF: tumor treatment fields.

Results of the final analysis of the EF-14 trial were similar to the interim analysis and are shown in Table 2. Both PFS and OS improved with the addition of TTF therapy to standard maintenance chemotherapy (ie, temozolomide). PFS increased

by 2.7 mo ($p < 0.001$) and OS increased by 4.9 mo ($p < 0.001$) in the TTF group. The time to a decrease in mental function was 2.5 months longer with TTF therapy ($p < 0.01$).

There was a similar percentage of dropouts at the final analysis—with 49 (11%) patients in the TTF group and 27 (12%) patients in the temozolomide alone group. More treatment cycles with temozolomide were administered in the TTF group (median, 6 for TTF group vs 5 for controls), a finding that is consistent with the longer PFS. Rates of adverse events were similar between the groups, including rates of seizures. In secondary analysis of patients who had not progressed, there was no reduction in health-related quality of life with TTF compared with temozolomide alone aside from “itchy skin”.¹² Interpretation of this result is limited by the low percentage of patients who completed the health-related quality of life assessments at follow-up (65.8% of the 655 patients alive at 3 months and 41.7% of the 473 patients alive at 12 months). A mixed-model analysis, which accounts for missing data, confirmed the results of the mean change from baseline analysis.

Table 2. Key Randomized Controlled Trial Results for Newly Diagnosed Glioblastoma

| Study | Final N (%) | Median PFS (95% CI), mo | Median OS (95% CI), mo | Systemic Adverse Events, n (%) | Seizures, n (%) | Time to 6-Point Decline in MMSE Score (95% CI), mo |
|----------------------------------------|-------------|-------------------------|------------------------|--------------------------------|-----------------|----------------------------------------------------|
| Stupp et al (2017)¹⁰ | | | | | | |
| TTF + temozolomide | 417 (89) | 6.7 (6.1 to 8.1) | 20.9 (19.3 to 22.7) | 218 (48) | 26 (6) | 16.7 (14.7 to 19.0) |
| Temozolomide alone | 202 (88) | 4.0 (3.8 to 4.4) | 16.0 (14.0 to 18.4) | 94 (44) | 13 (6) | 14.2 (12.7 to 17.0) |
| HR (95% CI) | | 0.63 (0.52 to 0.76) | 0.63 (0.53 to 0.76) | | | 0.79 (0.66 to 0.95) |
| P value | | <0.001 | <0.001 | 0.58 | | 0.01 |

CI: confidence interval; HR: hazard ratio; MMSE: Mini-Mental State Examination; OS: overall survival; PFS: progression-free survival; TTF: tumor-treatment fields.

Tables 3 and 4 display notable gaps identified in this trial, the major limitation is the lack of patient blinding to treatment assignment. However, PFS was assessed by investigators who were blinded to treatment and placebo effects on OS were expected to be minimal. Investigators considered it practically unfeasible (due to the heat and current of the TTF therapy) and ethically unacceptable to submit the control patients to repeated shaving of the head and continuous wear of a sham device over many months.

Table 3. Relevance Gaps

| Study; Trial | Population ^a | Intervention ^b | Comparator ^c | Outcomes ^d | Follow-Up ^e |
|----------------------------------------|-------------------------|---------------------------|----------------------------|-----------------------|------------------------|
| Stupp et al (2017) ¹⁰ ; EF- | | | 3. Possible differences in | | |

14

post-progression
treatment
affecting overall
survival

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 4. Study Design and Conduct Gaps

| Study; Trial | Allocation ^a | Blinding ^b | Selective Reporting ^c | Data Completeness ^d | Power ^e | Statistical ^f |
|------------------------------------------|-------------------------|------------------------------------------------------------|-------------------------------------|-----------------------------------|--------------------|--------------------------|
| Stupp et al (2017) ¹⁰ ; EF-14 | | 1. No sham control and not blinded to treatment assignment | | | | |

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM

The final analysis of the EF-14 trial, which included 695 patients from 83 sites, found a statistically and clinically significant increase of 2.7 months in PFS and an increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. There was no sham control, and patients were not blinded to treatment assignment, but PFS was assessed by blinded evaluators, and placebo effects on the objective measure of OS were likely to be minimal. There was no evidence of a negative impact of TTF therapy on health-related quality of life, except for itchy skin from the transducers.

TTF Therapy as an Adjunct or Alternative to Medical Therapy for Progressive or Recurrent GBM

Randomized Controlled Trials

The 2011 Food and Drug Administration approval of the NovoTTF-100A System (now called Optune) was based on a phase 3 multinational RCT (EF-11), results of which were published by Stupp et al (2012).⁴ This trial compared TTF therapy alone with physician's choice medical therapy in 237 adults who had relapsed or progressive glioblastoma (see Table 5). Patients had failed conventional treatment with radiotherapy, chemotherapy, and/or surgery, and more than 80% of participants had failed 2 or more prior chemotherapy regimens. In this trial, the term chemotherapy also applied to targeted agents such as bevacizumab. Patient characteristics and performance of additional post-recurrence debulking surgery were similar in the 2 groups.

Table 5. Summary of Key Randomized Controlled Trial Characteristics for Progressive or Recurrent Glioblastoma

| Study; Trial | Countries | Sites | Dates | Participants | Interventions | |
|----------------------------------------------|--------------------|-------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------------------------------------------------|
| | | | | | Active | Comparator |
| Stupp et al (2012)⁴; EF-11 | U.S., E.U., Israel | 28 | 1987-2013 | <ul style="list-style-type: none"> 237 adults with relapsed or progressive supratentorial glioblastoma KPS score $\geq 70\%$ | 120 patients treated with TTF alone, 93 (78%) completed 1 cycle | 117 patients treated with physician's choice of medical therapy ^a |

EU: European Union; KPS: Karnofsky Performance Status; TTF: tumor treating fields.

^a Medical therapy included bevacizumab, irinotecan, nitrosoureas, platinum-based chemotherapy (ie, carboplatin); temozolomide; or a combination of procarbazine, chloroethyl ether, and vincristine.

Participants were followed monthly, including laboratory tests. MRI images were evaluated at 2, 4, and 6 months from initiation of treatment, with subsequent MRIs performed according to local practice until disease progression. QOL questionnaires were completed every 3 months. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess mortality rates. The primary end point was OS. Secondary end points included PFS, the percentage of patients with PFS at 6 months, time to progression, 1-year survival rate, QOL, and radiologic response. All end points were evaluated using intention-to-treat analysis.

The trial did not reach its primary end point of improved survival compared with active medical therapy (see Table 6). With a median follow-up of 39 months, 93% of patients had died. There was not a statistically significant difference in survival rates at 1, 2, and 3 years between groups. Patients in the TTF group did not, however, suffer the typical systemic side effects of chemotherapy. The most common adverse event in the TTF group was grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids and did not require treatment breaks. Control participants experienced grade 2, 3, or 4 events by organ system

related to the pharmacologic activity of chemotherapy agents used. Hematologic events of grade 2 or greater were observed in 17% of chemotherapy patients compared with 3% of TTF patients. Gastrointestinal disorders of grade 2 or greater were identified in 17% of chemotherapy patients compared with 4% of TTF patients. Severe (grades 3-4) hematologic and gastrointestinal toxicity was observed in 7% of chemotherapy controls compared with 1% of the TTF group.

Longitudinal QOL data, available in 63 (27%) participants, showed no meaningful differences between groups for the domains of global health and social functioning. However, cognitive and emotional functioning domains favored TTF therapy. Symptom scale analysis was by treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration.

The trial had a number of limitations (see Tables 7 and 8), that included lack of blinding and high loss to follow-up. Discontinuation of TTF therapy occurred in 22% of patients due to noncompliance or inability to handle the device, usually within the first few days. In the control group, 21 (18%) patients did not return to the treatment site, and details on disease progression and toxicity were not available. Longitudinal QOL could be analyzed only for 27% of patients who remained on study therapy for 3 months. The trial was designed as a superiority trial and did not provide adequate evidence of noninferiority.

Table 6. Summary of Key Randomized Controlled Trial Results for Recurrent or Progressive Glioblastoma

| Study; Trial | LTFU, n (%) | Median OS, mo | Progression-Free Survival | | Overall Survival (95% CI), % | | |
|-----------------------------------------|----------------|---------------------|---------------------------|------------------------------------|---------------------------------|-------------|------------|
| | | | Median, mo | Rate at 6 Months (95% CI), % | 1 Year | 2 Years | 3 Years |
| Stupp et al (2012) ⁴ ; EF-11 | | | | | | | |
| TTF | 23 (22) | 6.6 | 2.2 | 21.4 (13.5 to 29.3) | 20 | 8 (4 to 13) | 4 (1 to 8) |
| PCC | 12 (18) | 6.0 | 2.1 | 15.1 (7.8 to 22.3) | 20 | 5 (3 to 10) | 1 (0 to 3) |
| HR (95% CI) | | 0.86 (0.66 to 1.12) | 0.81 (0.60 to 1.09) | | | | |
| P value | | 0.27 | 0.16 | 0.13 | | | |

CI: confidence interval; HR: hazard ratio; LTFU: loss to follow-up; PCC: physician's choice chemotherapy; TTF: tumor treating fields.

Table 7. Relevance Gaps

| Study | Population ^a | Intervention ^b | Comparator ^c | Outcomes ^d | Follow-Up ^e |
|----------------------------------------------|-------------------------|---------------------------|------------------------------------|-----------------------|------------------------|
| Stupp et al (2012)⁴; EF-11 | | | 2. Physician's choice chemotherapy | | |

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Gaps

| Study; Trial | Allocation ^a | Blinding ^b | Selective Reporting ^d | Data Completeness ^e | Power ^d | Statistical ^f |
|-----------------------------------------|-------------------------|----------------------------------------|-------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-------------------------------------------|
| Stupp et al (2012) ⁴ ; EF-11 | | 1. Not blinded to treatment assignment | | 1. 78% of TTF group completed only 1 cycle of therapy, 18% of control group lost to follow-up 1. Longitudinal QOL data were available for 27% of patients | | 1. Not designed as a noninferiority trial |

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

QOL: quality of life.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Nonrandomized Comparative Studies

Kesari et al (2017) conducted a post hoc analysis of the EF-14 trial (see Stupp et al [2017] above) to evaluate the efficacy of TTF in patients who had the first recurrence.¹³ Some patients in the temozolomide alone group crossed over to receive TTF plus chemotherapy after the first recurrence, resulting in 144 patients who received TTF fields plus chemotherapy and 60 patients who received chemotherapy alone for recurrent GBM (see Table 9). Patient characteristics and second-line treatments were well-balanced between the groups, with bevacizumab the most common second-line therapy. The median OS in patients treated with systemic therapy alone was 9.2 months (see Table 10). In comparison, the group

of patients who received TTF therapy in addition to systemic therapy had a median OS of 11.8 months ($p=0.043$).

A registry study published Mrugala et al (2014) assessed OS data from patients who received NovoTTF therapy in a real-world, clinical practice setting (see Table 9).¹⁴ Concurrent treatment was not captured in the registry, and it is possible that some patients received combination therapy. Median OS in the PRiDe clinical practice dataset (9.6 mo) was reported as superior to that attained in the EF-11 pivotal trial (6.6 mo, $p<0.001$) (see Table 10). More patients in the PRiDe registry were treated for first recurrence (33% vs 9%), and more had received bevacizumab as prior therapy (55% vs 19%). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

Table 9. Characteristics of Key Nonrandomized Trial Results

| Study | Study Type | Country | Dates | Participants | TTF | Controls | FU |
|-------------------------------------------|-------------------------|---------------------------------|-----------|-------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------|---------|
| Kesari et al (2017) ¹³ | EF-14 post hoc analysis | U.S., E.U., South Korea, Israel | 2009-2016 | 204 patients with first recurrence in the EF-14 trial | 144 patients treated with TTF plus second-line chemotherapy | 60 patients treated with second-line chemotherapy | 12.6 mo |
| Mrugala et al (2014) ¹⁴ | Registry | U.S. (91 centers) | 2011-2013 | 457 patients with recurrent GBM | Patient Registry Dataset (PRiDe) | EF-11 | |

FU: follow-up; GBM: glioblastoma; TTF: tumor treating fields.

Table 10. Summary of Key Nonrandomized Trial Results

| Study | Median OS, mo | Median OS With Bevacizumab, mo | |
|------------------------------------------------|---------------------|--------------------------------|---------------|
| Kesari et al (2017)¹³; EF-14 | | | |
| TTF plus chemotherapy | 11.8 | 11.8 | |
| Chemotherapy alone | 9.2 | 9.0 | |
| Hazard ratio (95% CI) | 0.70 (0.48 to 1.00) | 0.61 (0.37 to 0.99) | |
| P value | 0.049 | 0.043 | |
| | | 1-Year OS, % | 2-Year OS, %. |
| Mrugala et al (2014)¹⁴ | | | |
| PRiDe Registry | 9.6 | 44 | 30 |
| EF-11 | 6.6 | 20 | 9 |
| Hazard ratio (95% CI) | 0.66 (0.05 to 0.86) | | |
| P value | <0.001 | | |

CI: confidence interval; OS: overall survival, TTF: tumor treating fields.

Post hoc analyses of the EF-11 pivotal trial have been reported. Wong et al (2014) published a subgroup analysis to determine characteristics of responders and nonresponders in the active treatment and active treatment control.¹⁵ They found

that responders had a lower grade of histology and lower daily dexamethasone use than nonresponders. A second post hoc analysis by Kanner et al (2014) of the EF-11 pivotal trial data was performed to evaluate OS among patients who finished at least 1 complete course of TTF or chemotherapy.¹⁶ The investigators reported that median OS was 7.7 months in the TTF group compared with 5.9 months in the chemotherapy group ($p=0.009$). These post hoc analyses are considered to be hypothesis-generating.

Section Summary: TTF Therapy as an Adjunct or Alternative to Chemotherapy for Progressive or Recurrent GBM

The single RCT for TTF as an alternative to chemotherapy reported that outcomes following TTF therapy were similar to outcomes following standard chemotherapy. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. The noninferiority of TTF compared with chemotherapy might be considered a sufficient health benefit, if TTF reduced treatment toxicity. However, because the trial was not designed as a noninferiority trial no inferences of noninferiority compared with chemotherapy can be made. Physician's choice therapy during the trial was heterogeneous, although analysis indicated that survival was not affected by choice of chemotherapy. More patients in the TTF group than in the control group did not complete the treatment course. The number of patients who contributed QOL data was approximately one-quarter of total enrollment, and the self-reported QOL indicators might have been subject to bias due to the lack of blinding.

A nonrandomized post hoc evaluation of the EF-14 trial suggests that TTF may improve survival when combined with chemotherapy for recurrent GBM. This analysis should be considered hypothesis-generating, and further study in high-quality RCTs is needed.

Summary of Evidence

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes an RCT. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall

survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 3 physician specialty societies (one of which provided 6 responses and 2 of which provided 1 response each) and 1 academic medical center (total of 9 individual responses) while this policy was under review in 2016. There was majority support, but not consensus, for the use of tumor treatment fields therapy as an adjunct to maintenance treatment following initial therapy for glioblastoma multiforme. There was mixed support for the use of tumor treatment fields as an alternative to chemotherapy in advanced or recurrent glioblastoma multiforme.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2018) include recommendations for the treatment of glioblastoma (see Table 11).³ For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate O⁶-methylguanine-DNA methyltransferase promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric field therapy is a category 1 recommendation. Alternating electric currents therapy is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a category 2B recommendation.

Table 11. Guidelines for Adjuvant Treatment of Glioblastoma, by Age and Performance Status

| Age, y | KPS Score, % | Treatment Options | Category |
|--------|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| ≤70 | ≥60 | <ul style="list-style-type: none"> Standard RT plus concurrent and adjuvant temozolomide plus TTF Standard RT plus concurrent and adjuvant temozolomide | 1 |
| ≤70 | <60 | <ul style="list-style-type: none"> Hypofractionated RT with/without concurrent or adjuvant temozolomide Temozolomide Palliative/best supportive care | 2A |
| >70 | ≥60 | <ul style="list-style-type: none"> Hypofractionated RT plus concurrent and adjuvant temozolomide Standard RT plus concurrent and adjuvant temozolomide plus TTF Temozolomide alone Hypofractionated brain RT alone | 1 |
| >70 | <60 | <ul style="list-style-type: none"> Hypofractionated brain RT alone Temozolomide alone Palliative/best supportive care | 2A |

KPS: Karnofsky Performance Status; RT: radiotherapy; TTF: tumor treating fields.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 12. Of particular note are the phase 3 trials evaluating TTF therapy in non-small-cell lung cancer and pancreatic cancer. TTF therapy is an active area of research for mechanisms underlying its effects on cancer cells.

Table 12. Summary of Key Trials

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Ongoing | | | |
| NCT01971281^a | A Phase II Study of TTFields (150 kHz) Concomitant With Gemcitabine and TTFields Concomitant With Gemcitabine Plus Nab-paclitaxel for Front-line Therapy of Advanced Pancreatic Adenocarcinoma | 40 | Dec 2017 (ongoing) |
| NCT01894061^a | A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma | 40 | Dec 2018 |
| NCT02663271^a | A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the Combination of TTFields and Pulsed Bevacizumab Treatment in Patients With Bevacizumab-refractory | 18 | Mar 2019 |

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------------|
| NCT02831959 ^a | Recurrent Glioblastoma Pivotal, Open-label, Randomized Study of Radiosurgery With or Without Tumor Treating Fields (TTFields) (150kHz) for 1-10 Brain Metastases From Non-small Cell Lung Cancer (NSCLC) (METIS) | 270 | Jul 2019 |
| NCT02973789 ^a | LUNAR: Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields) Concurrent With Standard of Care Therapies for Treatment of Stage 4 Non-small Cell Lung Cancer (NSCLC) Following Platinum Failure | 534 | Dec 2021 |
| NCT02743078 ^a | Phase II Trial Of Optune® Plus Bevacizumab In Bevacizumab-Refractory, Recurrent Glioblastoma | 85 | Aug 2022 |
| NCT03377491 ^a | EF-27 Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields, 150kHz) Concomitant With Gemcitabine and Nab-paclitaxel for Front-line Treatment of Locally-advanced Pancreatic Adenocarcinoma (PANOVA-3) | 556 | Dec 2022 |

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

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Billing Coding/Physician Documentation Information

- A4555** Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
- E0766** Electrical stimulation device used for cancer treatment, includes all accessories, any type

ICD-10 Codes

- C71.0-** Malignant neoplasm of brain code range
- C71.9**

There are no specific codes for the initial application of this system or instruction on use. The patient reapplies the transducer arrays at home after the initial instruction.

There are HCPCS codes for the system and the transducer arrays:

E0766 Electrical stimulation device, used for cancer treatment, includes all accessories, any type

A4555 Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only.

Additional Policy Key Words

N/A

Policy Implementation/Update Information

- 12/1/13 New Policy; considered investigational.
- 12/1/14 No policy statement change
- 12/1/15 No policy statement changes.
- 12/1/16 Policy statements rewritten for clarity but tumor treating fields remains investigational for all indications.

- 12/1/17 Policy statements rewritten for clarity but tumor treating fields remains investigational for all indications.
- 9/1/18 Title changed from "Tumor Treatment Fields Therapy for Glioblastoma" to "Tumor Treating Fields Therapy". May be considered medically necessary in conjunction with maintenance temozolomide for patients with newly diagnosed glioblastoma multiforme. Investigational for all other indications.
-

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MP 1.01.529**Tumor -Treatment Fields Therapy for Glioblastoma****BCBSA Ref. Policy: 1.01.29****Last Review: 06/27/2018****Effective Date: 06/27/2018****Section: Durable Medical Equipment****Related Policies**

None

DISCLAIMER

Our medical policies are designed for informational purposes only and are not an authorization, or an explanation of benefits, or a contract. Receipt of benefits is subject to satisfaction of all terms and conditions of the coverage. Medical technology is constantly changing, and we reserve the right to review and update our policies periodically.

POLICY

The use of FDA approved devices to generate electric tumor treatment fields (TTF) to treat histologically confirmed supratentorial glioblastoma (known also as glioblastoma multiforme [GBM] or World Health Organization [WHO] grade IV astrocytoma) is considered **medically necessary** as adjunctive treatment when all of the following criteria below are met:

1. Initial treatment with de-bulking surgery or biopsy followed by chemoradiation with concomitant temozolomide and radiotherapy has been completed with no documented tumor progression (see Policy Guidelines); and
2. TTF is initiated within 7 weeks of chemoradiation; and
3. TTF is used in combination with temozolomide; and
4. Individual has Karnofsky Performance Status score of 60 or higher and
5. Individual or caregiver has been trained and is willing and able to apply and maintain the device at least 18 hours every day.

When the above criteria are met, treatment may be authorized for up to 6 months. For treatment to be considered **medically necessary** beyond that time, the following criteria must be met:

1. Documentation is provided of compliance with proper device use for at least 18 hours a day.
2. Disease progression is not occurring despite treatment with TTF (See Policy Guidelines).

The use of devices to generate electric tumor treatment fields (TTF) is considered **investigational** when the criteria above are not met and for all other indications.

POLICY GUIDELINES

Coverage for TTF may be allowed for up to 6 months with a medical necessity determination, and if the patient is shown to be compliant with the regimen. Continued use after 6 months will require additional documentation to show no progression of the tumor outside the radiation treatment field, worsening of the member's condition (e.g., Karnofsky performance status of < 60), or new symptoms of progressive disease.

Tumor progression may be radiologically defined as tumor growth greater than 25% compared to the

smallest measured tumor area or the appearance of one or more new GBM lesions in the brain. It is noted that pseudo-progression can appear as tumor progression on imaging and may actually be treatment effect. If pseudo-progression is identified, it must be supported through documentation by a neuro-radiologist.

There are no specific codes for the initial application of this system and instruction on use. The patient reapplies the transducer arrays at home after the initial instruction.

Effective in 2014, there are HCPCS codes for the system and the transducer arrays:

E0766: Electrical stimulation device, used for cancer treatment, includes all accessories, any type

A4555: Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only

Table 1. Karnofsky Performance Status Scale¹⁷

| Condition | Value (%) | Level of Functional Capacity |
|---------------------------------------------------------------------------------------------------------------------|-----------|--------------------------------------------------------------------------------|
| Able to carry on normal activity and to work; no special care needed | 100% | No complaints; no evidence of disease |
| | 90% | Able to carry on normal activity; minor signs or symptoms of disease |
| | 80% | Normal activity with effort; some signs or symptoms of disease |
| Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed | 70% | Cares for self; unable to carry on normal activity or to do active work |
| | 60% | Requires occasional assistance but is able to care for most personal needs |
| | 50% | Requires considerable assistance and frequent medical care |
| Unable to care for self; requires equivalent of institutional or hospital care; diseases may be progressing rapidly | 40% | Disabled; requires special care and assistance |
| | 30% | Severely disabled; hospital admission indicated although death not imminent |
| | 20% | Very sick; hospital admission necessary; active supportive treatment necessary |
| | 10% | Moribund; fatal processes progressing rapidly |
| | 0% | Dead |

BENEFIT APPLICATION

BLUE CARD/NATIONAL ACCOUNT ISSUES

State or federal mandates (e.g., FEP) may dictate that all U.S. Food and Drug Administration-approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only on the basis of their medical necessity.

BACKGROUND**GLIOBLASTOMA MULTIFORME**

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.¹ GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (eg, bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors.¹ The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to 1 year, and the 5-year survival rate was around 5%.²

Clinical Context and Therapy Purpose

The purpose of alternating electrical field therapy, more commonly known as tumor treating fields (TTF) therapy, is to provide a treatment option that is better than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

Treatment of Newly Diagnosed GBM

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these 2 therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles. Response and overall survival rates with temozolomide are higher in patients who have O6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation (see 2.04.113 on MGMT promoter methylation for malignant gliomas).

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice (see the Supplemental Information section).³ For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur essentially all patients.

Treatment of Recurrent GBM

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the

antivascular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (eg, lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at 6 months is less than 20%.⁴ There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

The questions addressed in this evidence review are:

- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

Interventions

TTF therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields.⁴⁻⁶ TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. TTF therapy is proposed to inhibit tumor growth by 2 mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase.^{5,6} Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune (formerly NovoTTF-100A System) is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

Comparators

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

The following practices are currently being used to make decisions about recurrent GBM: medical therapy.

TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds 3 to 5 months.⁴

Outcomes

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

Timing

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.

Setting

The setting is outpatient care by an oncologist or neuro-oncologist.

REGULATORY STATUS

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process.⁷ The FDA-approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, FDA approved Novocure's request for a product name change from NovoTTF-110A System to Optune®.⁸

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.⁹ The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

FDA product code: NZK.

RATIONALE

This evidence review was created in August 2013 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through April 5, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are

important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

For this review, 3 indications are evaluated: (1) tumor treating fields (TTF) as an adjunct to maintenance chemotherapy in newly diagnosed patients following initial treatment with surgery, radiotherapy and chemotherapy and (2) TTF as an adjunct or (3) alternative to medical therapy (eg, bevacizumab, chemotherapy) in progressive or recurrent glioblastoma multiforme (GBM).

Study Selection

The PICOTS was used to select relevant studies.

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Within each category of study design, studies with larger sample size studies and longer duration were sought.

TTF THERAPY AS AN ADJUNCT TO STANDARD MAINTENANCE CARE FOR NEWLY DIAGNOSED GBM

Randomized Controlled Trials

Stupp et al (2017) published results of the EF-14 multicenter, open-label phase 3 RCT that evaluated maintenance therapy with TTF for newly diagnosed GBM.¹⁰ The trial included 695 patients from 83 sites who had supratentorial GBM and had completed standard treatment consisting of biopsy or surgical resection followed by radiotherapy and chemotherapy (see Table 1). A Karnofsky Performance Status (KPS) score of 70 or higher was an additional inclusion criterion to ensure independence in activities of daily living, and patients with rapidly progressing GBM following radiochemotherapy were excluded from the trial. Patients were randomized in a 2:1 fashion to TTF plus maintenance temozolomide or maintenance temozolomide alone.

All patients were seen monthly for follow-up. Quality of life (QOL) was assessed every 3 months, and magnetic resonance imaging (MRI) was performed every 2 months until tumor progression. Tumor progression on MRI was adjudicated by a central review committee blinded to treatment group. The primary outcome was progression-free survival (PFS), and the secondary outcome was overall survival (OS). The analysis was by intention-to-treat, including 26 patients from the control arm who crossed over to TTF following the planned interim analysis.

In 2014, an independent data and safety monitoring board concluded from the planned interim analysis that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended

trial termination. The Food and Drug Administration approved the trial termination, and the trial was closed to recruitment with 695 of the planned 700 participants randomized. Control arm participants were allowed to cross over to the experimental treatment at this time. The interim analysis, which the Food and Drug Administration considered for the 2015 expanded approval of Optune, was published by Stupp et al (2015).¹¹ At the time of the interim analysis, data were available for 210 patients randomized to TTF plus temozolomide and 105 patients to temozolomide alone. Follow-up of the remainder of the 695 enrolled patients continued after enrollment was closed.

Table 1. Key Randomized Controlled Trial Characteristics for Newly Diagnosed Glioblastoma

| Study; Trial | Countries | Site | Dates | Participants | Interventions |
|------------------------------------------|---------------------------------|------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| | | | | | Active Comparator |
| Stupp et al (2017) ¹⁰ ; EF-14 | U.S., E.U., South Korea, Israel | 83 | 2009-2016 | <ul style="list-style-type: none"> 695 newly diagnosed with GBM and treated by radiochemotherapy KPS score ≥ 70 | TTF >18 h/d plus maintenance temozolomide (n=466) Maintenance temozolomide alone (5 d every 28 d for 6 cycles) (n=229) |

GBM: glioblastoma multiforme; h/d; hours per day; KPS: Karnofsky Performance Status; TTF: tumor treatment fields.

Results of the final analysis of the EF-14 trial were similar to the interim analysis and are shown in Table 2. Both PFS and OS improved with the addition of TTF therapy to standard maintenance chemotherapy (ie, temozolomide). PFS increased by 2.7 mo ($p < 0.001$) and OS increased by 4.9 mo ($p < 0.001$) in the TTF group. The time to a decrease in mental function was 2.5 months longer with TTF therapy ($p < 0.01$).

There was a similar percentage of dropouts at the final analysis—with 49 (11%) patients in the TTF group and 27 (12%) patients in the temozolomide alone group. More treatment cycles with temozolomide were administered in the TTF group (median, 6 for TTF group vs 5 for controls), a finding that is consistent with the longer PFS. Rates of adverse events were similar between the groups, including rates of seizures. In secondary analysis of patients who had not progressed, there was no reduction in health-related quality of life with TTF compared with temozolomide alone aside from “itchy skin”.¹² Interpretation of this result is limited by the low percentage of patients who completed the health-related quality of life assessments at follow-up (65.8% of the 655 patients alive at 3 months and 41.7% of the 473 patients alive at 12 months). A mixed-model analysis, which accounts for missing data, confirmed the results of the mean change from baseline analysis.

Table 2. Key Randomized Controlled Trial Results for Newly Diagnosed Glioblastoma

| Study | Final N (%) | Median PFS (95% CI), mo | Median OS (95% CI), mo | Systemic Adverse Events, n (%) | Seizures, n (%) | Time to 6-Point Decline in MMSE Score (95% CI), mo |
|----------------------------------|-------------|-------------------------|------------------------|--------------------------------|-----------------|----------------------------------------------------|
| Stupp et al (2017) ¹⁰ | | | | | | |
| TTF + temozolomide | 417 (89) | 6.7 (6.1 to 8.1) | 20.9 (19.3 to 22.7) | 218 (48) | 26 (6) | 16.7 (14.7 to 19.0) |

| | | | | | | |
|------------------------|----------|------------------------|------------------------|---------|--------|------------------------|
| Temozolomid e alone | 202 (88) | 4.0 (3.8 to 4.4) | 16.0 (14.0 to 18.4) | 94 (44) | 13 (6) | 14.2 (12.7 to 17.0) |
| HR (95% CI) | | 0.63 (0.52 to 0.76) | 0.63 (0.53 to 0.76) | | | 0.79 (0.66 to 0.95) |
| P value | | <0.001 | <0.001 | 0.58 | | 0.01 |

CI: confidence interval; HR: hazard ratio; MMSE: Mini-Mental State Examination; OS: overall survival; PFS: progression-free survival; TTF: tumor treatment fields.

Tables 3 and 4 display notable gaps identified in this trial, the major limitation is the lack of patient blinding to treatment assignment. However, PFS was assessed by investigators who were blinded to treatment and placebo effects on OS were expected to be minimal. Investigators considered it practically unfeasible (due to the heat and current of the TTF therapy) and ethically unacceptable to submit the control patients to repeated shaving of the head and continuous wear of a sham device over many months.

Table 3. Relevance Gaps

| Study; Trial | Population ^a | Intervention ^b | Comparator ^c | Outcome ^s ^d | Follow-Up ^e |
|---------------------------------------------|-------------------------|---------------------------|-----------------------------------------------------------------------------------------|-----------------------------------|------------------------|
| Stupp et al (2017) ¹⁰ ; EF-14 | | | 3. Possible differences in post- progression treatment affecting overall survival | | |

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 4. Study Design and Conduct Gaps

| Study; Trial | Allocation ^a | Blinding ^b | Selective Reporting ^c | Data Completeness ^d | Power ^e | Statistical ^f |
|------------------------------------------------|-------------------------|------------------------------------------------------------------------------|-------------------------------------|-----------------------------------|--------------------|--------------------------|
| Stupp et al (2017) ¹⁰ ; EF-14 | | 1. No sham control and not blinded to treatment assignment | | | | |

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM

The final analysis of the EF-14 trial, which included 695 patients from 83 sites, found a statistically and clinically significant increase of 2.7 months in PFS and an increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. There was no sham control, and patients were not blinded to treatment assignment, but PFS was assessed by blinded evaluators, and placebo effects on the objective measure of OS were likely to be minimal. There was no evidence of a negative impact of TTF therapy on health-related quality of life, except for itchy skin from the transducers.

TTF THERAPY AS AN ADJUNCT OR ALTERNATIVE TO MEDICAL THERAPY FOR PROGRESSIVE OR RECURRENT GBM

Randomized Controlled Trials

The 2011 Food and Drug Administration approval of the NovoTTF-100A System (now called Optune) was based on a phase 3 multinational RCT (EF-11), results of which were published by Stupp et al (2012).⁴ This trial compared TTF therapy alone with physician's choice medical therapy in 237 adults who had relapsed or progressive glioblastoma (see Table 5). Patients had failed conventional treatment with radiotherapy, chemotherapy, and/or surgery, and more than 80% of participants had failed 2 or more prior chemotherapy regimens. In this trial, the term chemotherapy also applied to targeted agents such as bevacizumab. Patient characteristics and performance of additional post-recurrence debulking surgery were similar in the 2 groups.

Table 5. Summary of Key Randomized Controlled Trial Characteristics for Progressive or Recurrent Glioblastoma

| Study; Trial | Countries | Sites | Dates | Participants | Interventions | |
|-----------------------------------------|--------------------|-------|-----------|-----------------------------------------------------------------------|-----------------------------------------------------------|------------------------------------------------------------------------------|
| | | | | | Active | Comparator |
| Stupp et al (2012) ⁴ ; EF-11 | U.S., E.U., Israel | 28 | 1987-2013 | • 237 adults with relapsed or progressive supratentorial glioblastoma | 120 patients treated with TTF alone, 93 (78%) completed 1 | 117 patients treated with physician's choice of medical therapy ^a |

• KPS score $\geq 70\%$ cycle

EU: European Union; KPS: Karnofsky Performance Status; TTF: tumor treating fields.

^a Medical therapy included bevacizumab, irinotecan, nitrosoureas, platinum-based chemotherapy (ie, carboplatin); temozolomide; or a combination of procarbazine, chloroethyl ether, and vincristine.

Participants were followed monthly, including laboratory tests. MRI images were evaluated at 2, 4, and 6 months from initiation of treatment, with subsequent MRIs performed according to local practice until disease progression. QOL questionnaires were completed every 3 months. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess mortality rates. The primary end point was OS. Secondary end points included PFS, the percentage of patients with PFS at 6 months, time to progression, 1-year survival rate, QOL, and radiologic response. All end points were evaluated using intention-to-treat analysis.

The trial did not reach its primary end point of improved survival compared with active medical therapy (see Table 6). With a median follow-up of 39 months, 93% of patients had died. There was not a statistically significant difference in survival rates at 1, 2, and 3 years between groups. Patients in the TTF group did not, however, suffer the typical systemic side effects of chemotherapy. The most common adverse event in the TTF group was grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids and did not require treatment breaks. Control participants experienced grade 2, 3, or 4 events by organ system related to the pharmacologic activity of chemotherapy agents used. Hematologic events of grade 2 or greater were observed in 17% of chemotherapy patients compared with 3% of TTF patients. Gastrointestinal disorders of grade 2 or greater were identified in 17% of chemotherapy patients compared with 4% of TTF patients. Severe (grades 3-4) hematologic and gastrointestinal toxicity was observed in 7% of chemotherapy controls compared with 1% of the TTF group.

Longitudinal QOL data, available in 63 (27%) participants, showed no meaningful differences between groups for the domains of global health and social functioning. However, cognitive and emotional functioning domains favored TTF therapy. Symptom scale analysis was by treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration.

The trial had a number of limitations (see Tables 7 and 8), that included lack of blinding and high loss to follow-up. Discontinuation of TTF therapy occurred in 22% of patients due to noncompliance or inability to handle the device, usually within the first few days. In the control group, 21 (18%) patients did not return to the treatment site, and details on disease progression and toxicity were not available. Longitudinal QOL could be analyzed only for 27% of patients who remained on study therapy for 3 months. The trial was designed as a superiority trial and did not provide adequate evidence of noninferiority.

Table 6. Summary of Key Randomized Controlled Trial Results for Recurrent or Progressive Glioblastoma

| Study; Trial | LTFU, n (%) | Median OS, mo | Progression-Free Survival | | Overall Survival (95% CI), % | | |
|---------------------------------------|-------------|---------------|---------------------------|------------------------------|------------------------------|---------|---------|
| | | | Median, mo | Rate at 6 Months (95% CI), % | 1 Year | 2 Years | 3 Years |
| Stupp et al (2012) ^a ; EF- | | | | | | | |

| | | | | | | | |
|-------------|---------|---------------------|---------------------|---------------------|----|-------------|------------|
| 11 | | | | | | | |
| TTF | 23 (22) | 6.6 | 2.2 | 21.4 (13.5 to 29.3) | 20 | 8 (4 to 13) | 4 (1 to 8) |
| PCC | 12 (18) | 6.0 | 2.1 | 15.1 (7.8 to 22.3) | 20 | 5 (3 to 10) | 1 (0 to 3) |
| HR (95% CI) | | 0.86 (0.66 to 1.12) | 0.81 (0.60 to 1.09) | | | | |
| P value | | 0.27 | 0.16 | 0.13 | | | |

CI: confidence interval; HR: hazard ratio; LTFU: loss to follow-up; PCC: physician's choice chemotherapy; TTF: tumor treating fields.

Table 7. Relevance Gaps

| Study | Population ^a | Intervention ^b | Comparator ^c | Outcomes ^d | Follow-Up ^e |
|-----------------------------------------|-------------------------|---------------------------|------------------------------------|-----------------------|------------------------|
| Stupp et al (2012) ⁴ ; EF-11 | | | 2. Physician's choice chemotherapy | | |

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Gaps

| Study; Trial | Allocation ^a | Blinding ^b | Selective Reporting ^d | Data Completeness ^e | Power ^d | Statistical ^f |
|-----------------------------------------|-------------------------|----------------------------------------|-------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-------------------------------------------|
| Stupp et al (2012) ⁴ ; EF-11 | | 1. Not blinded to treatment assignment | | 1. 78% of TTF group completed only 1 cycle of therapy, 18% of control group lost to follow-up 1. Longitudinal QOL data were available for 27% of patients | | 1. Not designed as a noninferiority trial |

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

QOL: quality of life.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Nonrandomized Comparative Studies

Kesari et al (2017) conducted a post hoc analysis of the EF-14 trial (see Stupp et al [2017] above) to evaluate the efficacy of TTF in patients who had the first recurrence.¹³ Some patients in the temozolomide alone group crossed over to receive TTF plus chemotherapy after the first recurrence, resulting in 144 patients who received TTF fields plus chemotherapy and 60 patients who received chemotherapy alone for recurrent GBM (see Table 9). Patient characteristics and second-line treatments were well-balanced between the groups, with bevacizumab the most common second-line therapy. The median OS in patients treated with systemic therapy alone was 9.2 months (see Table 10). In comparison, the group of patients who received TTF therapy in addition to systemic therapy had a median OS of 11.8 months ($p=0.043$).

A registry study published Mrugala et al (2014) assessed OS data from patients who received NovoTTF therapy in a real-world, clinical practice setting (see Table 9).¹⁴ Concurrent treatment was not captured in the registry, and it is possible that some patients received combination therapy. Median OS in the PRiDe clinical practice dataset (9.6 mo) was reported as superior to that attained in the EF-11 pivotal trial (6.6 mo, $p<0.001$) (see Table 10). More patients in the PRiDe registry were treated for first recurrence (33% vs 9%), and more had received bevacizumab as prior therapy (55% vs 19%). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

Table 9. Characteristics of Key Nonrandomized Trial Results

| Study | Study Type | Country | Dates | Participants | TTF | Controls | FU |
|------------------------------------|-------------------------|---------------------------------|-----------|-------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------|---------|
| Kesari et al (2017) ¹³ | EF-14 post hoc analysis | U.S., E.U., South Korea, Israel | 2009-2016 | 204 patients with first recurrence in the EF-14 trial | 144 patients treated with TTF plus second-line chemotherapy | 60 patients treated with second-line chemotherapy | 12.6 mo |
| Mrugala et al (2014) ¹⁴ | Registry | U.S. (91 centers) | 2011-2013 | 457 patients with recurrent GBM | Patient Registry Dataset (PRiDe) | EF-11 | |

FU: follow-up; GBM: glioblastoma; TTF: tumor treating fields.

Table 10. Summary of Key Nonrandomized Trial Results

| Study | Median OS, mo | Median OS With Bevacizumab, mo |
|-------|---------------|--------------------------------|
|-------|---------------|--------------------------------|

| | | | |
|-------------------------------------------|---------------------|---------------------|--------------|
| Kesari et al (2017) ¹³ ; EF-14 | | | |
| TTF plus chemotherapy | 11.8 | 11.8 | |
| Chemotherapy alone | 9.2 | 9.0 | |
| Hazard ratio (95% CI) | 0.70 (0.48 to 1.00) | 0.61 (0.37 to 0.99) | |
| P value | 0.049 | 0.043 | |
| | | 1-Year OS, % | 2-Year OS, % |
| Mrugala et al (2014) ¹⁴ | | | |
| PRiDe Registry | 9.6 | 44 | 30 |
| EF-11 | 6.6 | 20 | 9 |
| Hazard ratio (95% CI) | 0.66 (0.05 to 0.86) | | |
| P value | <0.001 | | |

CI: confidence interval; OS: overall survival, TTF: tumor treating fields.

Post hoc analyses of the EF-11 pivotal trial have been reported. Wong et al (2014) published a subgroup analysis to determine characteristics of responders and nonresponders in the active treatment and active treatment control.¹⁵ They found that responders had a lower grade of histology and lower daily dexamethasone use than nonresponders. A second post hoc analysis by Kanner et al (2014) of the EF-11 pivotal trial data was performed to evaluate OS among patients who finished at least 1 complete course of TTF or chemotherapy.¹⁶ The investigators reported that median OS was 7.7 months in the TTF group compared with 5.9 months in the chemotherapy group ($p=0.009$). These post hoc analyses are considered to be hypothesis-generating.

Section Summary: TTF Therapy as an Adjunct or Alternative to Chemotherapy for Progressive or Recurrent GBM

The single RCT for TTF as an alternative to chemotherapy reported that outcomes following TTF therapy were similar to outcomes following standard chemotherapy. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. The noninferiority of TTF compared with chemotherapy might be considered a sufficient health benefit, if TTF reduced treatment toxicity. However, because the trial was not designed as a noninferiority trial no inferences of noninferiority compared with chemotherapy can be made. Physician's choice therapy during the trial was heterogeneous, although analysis indicated that survival was not affected by choice of chemotherapy. More patients in the TTF group than in the control group did not complete the treatment course. The number of patients who contributed QOL data was approximately one-quarter of total enrollment, and the self-reported QOL indicators might have been subject to bias due to the lack of blinding.

A nonrandomized post hoc evaluation of the EF-14 trial suggests that TTF may improve survival when combined with chemotherapy for recurrent GBM. This analysis should be considered hypothesis-generating, and further study in high-quality RCTs is needed.

SUMMARY OF EVIDENCE

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes an RCT. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was

assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 3 physician specialty societies (one of which provided 6 responses and 2 of which provided 1 response each) and 1 academic medical center (total of 9 individual responses) while this policy was under review in 2016. There was majority support, but not consensus, for use of tumor treatment field's therapy as an adjunct to maintenance treatment following initial therapy for glioblastoma multiforme. There was mixed support for use of tumor treatment fields as an alternative to chemotherapy in advanced or recurrent glioblastoma multiforme.

PRACTICE GUIDELINES AND POSITION STATEMENTS National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2018) include recommendations for the treatment of glioblastoma (see Table 11).³ For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate O⁶-methylguanine-DNA methyltransferase promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric field therapy is a category 1 recommendation. Alternating electric currents therapy is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a category 2B recommendation.

Table 11. Guidelines for Adjuvant Treatment of Glioblastoma, by Age and Performance Status

| Age, y | KPS | | Treatment Options | Category |
|--------|----------|------------------------------------------------------------------|-------------------|----------|
| | Score, % | | | |
| ≤70 | ≥60 | • Standard RT plus concurrent and adjuvant temozolomide plus TTF | | 1 |

| | | | |
|-----|-----|------------------------------------------------------------------------|----|
| | | • Standard RT plus concurrent and adjuvant temozolomide | |
| ≤70 | <60 | • Hypofractionated RT with/without concurrent or adjuvant temozolomide | 2A |
| | | • Temozolomide | |
| | | • Palliative/best supportive care | |
| >70 | ≥60 | • Hypofractionated RT plus concurrent and adjuvant temozolomide | 1 |
| | | • Standard RT plus concurrent and adjuvant temozolomide plus TTF | |
| | | • Temozolomide alone | |
| | | • Hypofractionated brain RT alone | |
| >70 | <60 | • Hypofractionated brain RT alone | 2A |
| | | • Temozolomide alone | |
| | | • Palliative/best supportive care | |

KPS: Karnofsky Performance Status; RT: radiotherapy; TTF: tumor treating fields.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

MEDICARE NATIONAL COVERAGE

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 12. Of particular note are the phase 3 trials evaluating TTF therapy in non-small-cell lung cancer and pancreatic cancer. TTF therapy is an active area of research for mechanisms underlying its effects on cancer cells.

Table 12. Summary of Key Trials

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Ongoing | | | |
| NCT01971281 ^a | A Phase II Study of TTFields (150 kHz) Concomitant With Gemcitabine and TTFields Concomitant With Gemcitabine Plus Nab-paclitaxel for Front-line Therapy of Advanced Pancreatic Adenocarcinoma | 40 | Dec 2017 (ongoing) |
| NCT01894061 ^a | A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma | 40 | Dec 2018 |
| NCT02663271 ^a | A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the Combination of TTFields and Pulsed Bevacizumab Treatment in Patients With Bevacizumab-refractory Recurrent Glioblastoma | 18 | Mar 2019 |
| NCT02831959 ^a | Pivotal, Open-label, Randomized Study of Radiosurgery With or Without Tumor Treating Fields (TTFields) (150kHz) for 1-10 Brain Metastases From Non-small Cell Lung Cancer (NSCLC) (METIS) | 270 | Jul 2019 |

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------------|
| NCT02973789 ^a | LUNAR: Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields) Concurrent With Standard of Care Therapies for Treatment of Stage 4 Non-small Cell Lung Cancer (NSCLC) Following Platinum Failure | 534 | Dec 2021 |
| NCT02743078 ^a | Phase II Trial Of Optune® Plus Bevacizumab In Bevacizumab-Refractory Recurrent Glioblastoma | 85 | Aug 2022 |
| NCT03377491 ^a | EF-27 Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields, 150kHz) Concomitant With Gemcitabine and Nab-paclitaxel for Front-line Treatment of Locally-advanced Pancreatic Adenocarcinoma (PANOVA-3) | 556 | Dec 2022 |

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

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CODES

| Codes | Number | Description |
|------------------|-------------|----------------------------------------------------------------------------------------------------------------|
| CPT Codes | | No specific CPT code- See Policy Guidelines |
| | 191.0-191.9 | Malignant neoplasm of brain code range |
| HCPCS Codes | A4555 | Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only |
| | E0766 | Electrical stimulation device, used for cancer treatment, includes all accessories, any type |
| ICD-10-CM | | Investigational for all relevant diagnoses |
| | C71.0-C71.9 | Malignant neoplasm of brain code range |
| ICD-10-PCS | | Not applicable. Policy is only for outpatient services. ICD-10-PCS codes are only used for inpatient services. |
| Type of Service | | |
| Place of Service | | |

POLICY HISTORY

| Date | Action | Description |
|----------|----------------|--------------------------------------------------------------|
| 08/14/14 | Replace policy | Policy updated with literature review through June 26, 2014. |

Original Policy Date: August 2013

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| | | |
|------------|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | | References 8 and 16-17 added. Editorial revisions made to rationale section. Policy statement unchanged. |
| 08/13/15 | Replace policy | Policy updated with literature review through July 8, 2015; references 10-11 removed and 10-12 added. Policy statement unchanged. |
| 08/11/16 | Replace policy | Policy updated with literature review through July 18, 2016, and results of clinical vetting; reference 13 added. Policy statements rewritten for clarity but tumor treating fields remains investigational for all indications. |
| 12/23/2016 | Replace policy | Blue Cross of Idaho adopted new policy statement and policy guidelines to reflect NCCN 2A recommendations. Medically necessary indication with specific criteria. |
| 07/25/17 | Replace policy | Blue Cross of Idaho adopted changes as noted, with no change to policy statements. Policy updated with literature review through June 5, 2017; no references added. No change to policy statements or policy guidelines. |
| 03/29/18 | Update only | Medical policy renumbered from 1.01.29 to 1.01.529. |
| 06/27/18 | Replace policy | Policy updated with literature review through April 5, 2018; references 10, and 12-13, and 17 added. No change to policy statements or policy guidelines. |

Protocol

Tumor Treating Fields Therapy

(10129)

(Formerly Tumor Treatment Fields Therapy for Glioblastoma)

| | | |
|------------------|--------------------------|-------------------------------------------------|
| Medical Benefit | Effective Date: 10/01/18 | Next Review Date: 07/19 |
| Preauthorization | Yes | Review Dates: 09/15, 05/16, 09/16, 09/17, 07/18 |

Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

| Populations | Interventions | Comparators | Outcomes |
|------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Individuals: <ul style="list-style-type: none">• With newly diagnosed glioblastoma multiforme on maintenance therapy after initial treatment | Interventions of interest are: <ul style="list-style-type: none">• Tumor treating fields therapy as an adjunct to standard maintenance therapy | Comparators of interest are: <ul style="list-style-type: none">• Standard maintenance therapy alone | Relevant outcomes include: <ul style="list-style-type: none">• Overall survival• Disease-specific survival• Quality of life• Treatment-related morbidity |
| Individuals: <ul style="list-style-type: none">• With progressive or recurrent glioblastoma multiforme | Interventions of interest are: <ul style="list-style-type: none">• Tumor treating fields therapy as an adjunct or alternative to medical therapy | Comparators of interest are: <ul style="list-style-type: none">• Standard medical therapy | Relevant outcomes include: <ul style="list-style-type: none">• Overall survival• Disease-specific survival• Quality of life• Treatment-related morbidity |

DESCRIPTION

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

SUMMARY OF EVIDENCE

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes a randomized controlled trial (RCT). Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (i.e., temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited.

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The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

Tumor treating fields therapy to treat glioblastoma multiforme is considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:

- Adult patients ≥ 22 years of age
- Supratentorial tumor
- Karnofsky Performance Status score $\geq 70\%$
- Patient understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the Food and Drug Administration label (see Policy Guidelines).

Tumor treating fields therapy is considered **investigational** in all other conditions, including but not limited to the following situations:

- As an adjunct to standard medical therapy (e.g., bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
- For brain metastases
- For cancer in areas other than the brain.

POLICY GUIDELINES

Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth $> 25\%$ compared with the smallest tumor area measured in the patient during the trial or appearance of one or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).

The Food and Drug Administration label includes the following notices:

- Patients should use Optune for at least 18 hours a day to get the best response to treatment
- Patients should finish at least four full weeks of therapy to get the best response to treatment. Stopping treatment before four weeks lowers the chances of a response to treatment.

MEDICARE ADVANTAGE

For Medicare Advantage tumor-treatment fields therapy is considered **not medically necessary**.

BACKGROUND

GLIOBLASTOMA MULTIFORME

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.¹ GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (e.g., bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors.¹ The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to one year, and the five-year survival rate was around 5%.²

Clinical Context and Therapy Purpose

The purpose of alternating electrical field therapy, more commonly known as TTF therapy, is to provide a treatment option that is better than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

Treatment of Newly Diagnosed GBM

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these two therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for five days of every 28-day cycle for six cycles. Response and overall survival rates with temozolomide are higher in patients who have O6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation.

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice.³ For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur essentially all patients.

Treatment of Recurrent GBM

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivascular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (e.g., lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at six months is less than 20%.⁴ There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

The questions addressed in this protocol are:

- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

Interventions

TTF therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields.⁴⁻⁶ TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. TTF therapy is proposed to inhibit tumor growth by two mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase.^{5,6} Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune (formerly NovoTTF-100A System) is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma,⁴ disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and two to three days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is one month, with the continuation of treatment available until recurrence.

Comparators

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

The following practices are currently being used to make decisions about recurrent GBM: medical therapy.

TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds three to five months.⁴

Outcomes

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

Timing

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.

Setting

The setting is outpatient care by an oncologist or neuro-oncologist.

REGULATORY STATUS

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process.⁷ The FDA-approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, the FDA approved Novocure's request for a product name change from NovoTTF-110A System to Optune®.⁸

In October 2015, the FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.⁹ The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

FDA product code: NZK.

RELATED PROTOCOLS

Intensity-Modulated Radiotherapy: Central Nervous System Tumors

Intracavitary Balloon Catheter Brain Brachytherapy for Malignant Gliomas

Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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| | | | |
|------------------------------|--------------------------------------|------------------------|------------------|
| 1.01.29 | Tumor Treating Fields Therapy | | |
| Original Policy Date: | October 31, 2014 | Effective Date: | November 1, 2018 |
| Section: | 1.0 Durable Medical Equipment | Page: | Page 1 of 16 |

Policy Statement

Tumor treating fields therapy to treat glioblastoma multiforme may be considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in patients with **newly diagnosed** glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:

- Adult patients 18 years old or older
- Supratentorial tumor
- Karnofsky Performance Status score greater than or equal to 60%
- Documentation the patient understands device use, including the requirement for a shaved head, use for at least 18 hours a day for a minimum of 4 weeks, and is willing to comply with use criteria according to the Food and Drug Administration label (see Policy Guidelines section)

Tumor treating fields therapy is considered **investigational** in all other conditions, including but not limited to the following situations:

- As an adjunct or alternative to standard medical therapy for progressive or recurrent tumors (e.g., bevacizumab, chemotherapy) for patients with **progressive or recurrent** glioblastoma multiforme* (see Policy Guidelines section)
- For brain metastases
- For cancer in areas other than the brain

Policy Guidelines

*Use for progressive or recurrent disease is a level 2B recommendation in NCCN guidelines (as compared to level 1 for newly diagnosed). Typically, a category 1 or 2A recommendation is followed, but not 2B. Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth greater than 25% compared with the smallest tumor area measured in the patient during the trial or appearance of 1 or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).

The Food and Drug Administration label includes the following notices:

- Patients should use Optune for at least 18 hours a day to get the best response to treatment
- Patients should finish at least 4 full weeks of therapy to get the best response to treatment. Stopping treatment before 4 weeks lowers the chances of a response to treatment

Coding

There are no specific codes for the initial application of this system or instruction on use. The patient reapplies the transducer arrays at home after the initial instruction.

There are HCPCS codes for the system and the transducer arrays:

- **A4555**: Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
- **ED766**: Electrical stimulation device used for cancer treatment, includes all accessories, any type

Description

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

Related Policies

- Analysis of MGMT Promoter Methylation in Malignant Gliomas
- Intensity-Modulated Radiotherapy: Central Nervous System Tumors
- Intracavitary Balloon Catheter Brain Brachytherapy for Malignant Gliomas or Metastasis to the Brain
- Intraoperative Radiotherapy
- Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process.⁷ The FDA-approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

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The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients

with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

FDA product code: NZK.

Rationale

Background

Glioblastoma Multiforme

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.¹ GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (e.g., bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors.¹ The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to 1 year, and the 5-year survival rate was around 5%.²

Clinical Context and Therapy Purpose

The purpose of alternating electrical field therapy, more commonly known as tumor treating fields (TTF) therapy, is to provide a treatment option that is better than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

Treatment of Newly Diagnosed Glioblastoma Multiforme

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these 2 therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles. Response and overall survival rates with temozolomide are higher in patients who have O⁶-methylguanine-DNA methyltransferase (*MGMT*) gene promoter methylation (see Blue Shield of California Medical Policy: Analysis of MGMT Promoter Methylation in Malignant Gliomas on *MGMT* promoter methylation for malignant gliomas).

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice (see the Supplemental Information section).³ For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur essentially all patients.

Treatment of Recurrent Glioblastoma Multiforme

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivascular endothelial growth factor drug

bevacizumab, alkylating agents such as nitrosoureas (e.g., lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at 6 months is less than 20%.⁴ There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

The questions addressed in this evidence review are:

- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

Interventions

TTF therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields.⁴⁻⁶ TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. TTF therapy is proposed to inhibit tumor growth by 2 mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase.^{5,6} Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune (formerly NovoTTF-100A System) is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

Comparators

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

The following practices are currently being used to make decisions about recurrent GBM: medical therapy.

TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds 3 to 5 months.⁴

Outcomes

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

Timing

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.

Setting

The setting is outpatient care by an oncologist or neuro-oncologist.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

For this review, 3 indications are evaluated: (1) tumor treating fields (TTF) as an adjunct to maintenance chemotherapy in newly diagnosed patients following initial treatment with surgery, radiotherapy and chemotherapy and (2) TTF as an adjunct or (3) alternative to medical therapy (e.g., bevacizumab, chemotherapy) in progressive or recurrent glioblastoma multiforme (GBM).

Study Selection

The PICOTS was used to select relevant studies.

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Within each category of study design, studies with larger sample size studies and longer duration were sought.

TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM

Randomized Controlled Trials

Stupp et al (2017) published results of the EF-14 multicenter, open-label phase 3 RCT that evaluated maintenance therapy with TTF for newly diagnosed GBM.¹⁰ The trial included 695 patients from 83 sites who had supratentorial GBM and had completed standard treatment consisting of biopsy or surgical resection followed by radiotherapy and chemotherapy (see Table 1). A Karnofsky Performance Status (KPS) score of 70 or higher was an additional inclusion

criterion to ensure independence in activities of daily living, and patients with rapidly progressing GBM following radiochemotherapy were excluded from the trial. Patients were randomized in a 2:1 fashion to TTF plus maintenance temozolomide or maintenance temozolomide alone.

All patients were seen monthly for follow-up. Quality of life (QOL) was assessed every 3 months, and magnetic resonance imaging (MRI) was performed every 2 months until tumor progression. Tumor progression on MRI was adjudicated by a central review committee blinded to treatment group. The primary outcome was progression-free survival (PFS), and the secondary outcome was overall survival (OS). The analysis was by intention-to-treat, including 26 patients from the control arm who crossed over to TTF following the planned interim analysis.

In 2014, an independent data and safety monitoring board concluded from the planned interim analysis that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended trial termination. The Food and Drug Administration approved the trial termination, and the trial was closed to recruitment with 695 of the planned 700 participants randomized. Control arm participants were allowed to cross over to the experimental treatment at this time. The interim analysis, which the Food and Drug Administration considered for the 2015 expanded approval of Optune, was published by Stupp et al (2015).¹¹ At the time of the interim analysis, data were available for 210 patients randomized to TTF plus temozolomide and 105 patients to temozolomide alone. Follow-up of the remainder of the 695 enrolled patients continued after enrollment was closed.

Table 1. Key Randomized Controlled Trial Characteristics for Newly Diagnosed Glioblastoma

| Study; Trial | Countries | Sites | Dates | Participants | Interventions | |
|------------------------------------------|---------------------------------|-------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|----------------------------------------------------------------------|
| | | | | | Active | Comparator |
| Stupp et al (2017) ¹⁰ ; EF-14 | U.S., E.U., South Korea, Israel | 83 | 2009-2016 | <ul style="list-style-type: none"> 695 newly diagnosed with GBM and treated by radiochemotherapy KPS score ≥ 70 | TTF >18 h/d plus maintenance temozolomide (n=466) | Maintenance temozolomide alone (5 d every 28 d for 6 cycles) (n=229) |

GBM: glioblastoma multiforme; h/d; hours per day; KPS: Karnofsky Performance Status; TTF: tumor treatment fields.

Results of the final analysis of the EF-14 trial were similar to the interim analysis and are shown in Table 2. Both PFS and OS improved with the addition of TTF therapy to standard maintenance chemotherapy (i.e., temozolomide). PFS increased by 2.7 mo ($p < 0.001$) and OS increased by 4.9 mo ($p < 0.001$) in the TTF group. The time to a decrease in mental function was 2.5 months longer with TTF therapy ($p < 0.01$).

There was a similar percentage of dropouts at the final analysis—with 49 (11%) patients in the TTF group and 27 (12%) patients in the temozolomide alone group. More treatment cycles with temozolomide were administered in the TTF group (median, 6 for TTF group vs 5 for controls), a finding that is consistent with the longer PFS. Rates of adverse events were similar between the groups, including rates of seizures. In secondary analysis of patients who had not progressed, there was no reduction in health-related quality of life with TTF compared with temozolomide alone aside from "itchy skin".¹² Interpretation of this result is limited by the low percentage of patients who completed the health-related quality of life assessments at follow-up (65.8% of the 655 patients alive at 3 months and 41.7% of the 473 patients alive at 12 months). A mixed-model analysis, which accounts for missing data, confirmed the results of the mean change from baseline analysis.

Table 2. Key Randomized Controlled Trial Results for Newly Diagnosed Glioblastoma

| Study | Final N (%) | Median PFS (95% CI, mo) | Median OS (95% CI, mo) | Systemic Adverse Events, n (%) | Seizures, n (%) | Time to 6-Point Decline in MMSE Score (95% CI, mo) |
|-------------------------------------|-------------|----------------------------|---------------------------|--------------------------------------|--------------------|----------------------------------------------------------|
| Stupp et al (2017) ¹⁰ | | | | | | |
| TTF + temozolomide | 417 (89) | 6.7 (6.1 to 8.1) | 20.9 (19.3 to 22.7) | 218 (48) | 26 (6) | 16.7 (14.7 to 19.0) |
| Temozolomide alone | 202 (88) | 4.0 (3.8 to 4.4) | 16.0 (14.0 to 18.4) | 94 (44) | 13 (6) | 14.2 (12.7 to 17.0) |
| HR (95% CI) | | 0.63 (0.52 to 0.76) | 0.63 (0.53 to 0.76) | | | 0.79 (0.66 to 0.95) |
| P value | | <0.001 | <0.001 | 0.58 | | 0.01 |

CI: confidence interval; HR: hazard ratio; MMSE: Mini-Mental State Examination; OS: overall survival; PFS: progression-free survival; TTF: tumor treatment fields.

Tables 3 and 4 display notable gaps identified in this trial, the major limitation is the lack of patient blinding to treatment assignment. However, PFS was assessed by investigators who were blinded to treatment and placebo effects on OS were expected to be minimal. Investigators considered it practically unfeasible (due to the heat and current of the TTF therapy) and ethically unacceptable to submit the control patients to repeated shaving of the head and continuous wear of a sham device over many months.

Table 3. Relevance Gaps

| Study; Trial | Population ^a | Intervention ^b | Comparator ^c | Outcomes ^d | Follow-Up ^e |
|---------------------------------------------|-------------------------|---------------------------|----------------------------------------------------------------------------------|-----------------------|------------------------|
| Stupp et al (2017) ¹⁰ ; EF-14 | | | 3. Possible differences in post-progression treatment affecting overall survival | | |

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 4. Study Design and Conduct Gaps

| Study; Trial | Allocation ^a | Blinding ^b | Selective Reporting ^c | Data Completeness ^d | Power ^e | Statistical |
|---------------------------------------------|-------------------------|------------------------------------------------------------|-------------------------------------|-----------------------------------|--------------------|-------------|
| Stupp et al (2017) ¹⁰ ; EF-14 | | 1. No sham control and not blinded to treatment assignment | | | | |

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: TTF Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed GBM

The final analysis of the EF-14 trial, which included 695 patients from 83 sites, found a statistically and clinically significant increase of 2.7 months in PFS and an increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (i.e., temozolomide) in patients with newly diagnosed GBM. There was no sham control, and patients were not blinded to treatment assignment, but PFS was assessed by blinded evaluators, and placebo effects on the objective measure of OS were likely to be minimal. There was no evidence of a negative impact of TTF therapy on health-related quality of life, except for itchy skin from the transducers.

TTF Therapy as an Adjunct or Alternative to Medical Therapy for Progressive or Recurrent GBM Randomized Controlled Trials

The 2011 Food and Drug Administration approval of the NovoTTF-100A System (now called Optune) was based on a phase 3 multinational RCT (EF-11), results of which were published by Stupp et al (2012).⁴ This trial compared TTF therapy alone with physician's choice medical therapy in 237 adults who had relapsed or progressive glioblastoma (see Table 5). Patients had failed conventional treatment with radiotherapy, chemotherapy, and/or surgery, and more than 80% of participants had failed 2 or more prior chemotherapy regimens. In this trial, the term chemotherapy also applied to targeted agents such as bevacizumab. Patient characteristics and performance of additional post-recurrence debulking surgery were similar in the 2 groups.

Table 5. Summary of Key Randomized Controlled Trial Characteristics for Progressive or Recurrent Glioblastoma

| Study; Trial | Countries | Sites | Dates | Participants | Interventions | |
|-----------------------------------------|--------------------|-------|-----------|--------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------------------------------------------------|
| | | | | | Active | Comparator |
| Stupp et al (2012) ⁴ ; EF-11 | U.S., E.U., Israel | 28 | 1987-2013 | • 237 adults with relapsed or progressive supratentorial glioblastoma • KPS score $\geq 70\%$ | 120 patients treated with TTF alone, 93 (78%) completed 1 cycle | 117 patients treated with physician's choice of medical therapy ^a |

EU: European Union; KPS: Karnofsky Performance Status; TTF: tumor treating fields.

^a Medical therapy included bevacizumab, irinotecan, nitrosoureas, platinum-based chemotherapy (i.e., carboplatin); temozolomide; or a combination of procarbazine, chloroethyl ether, and vincristine.

Participants were followed monthly, including laboratory tests. MRI images were evaluated at 2, 4, and 6 months from initiation of treatment, with subsequent MRIs performed according to local practice until disease progression. QOL questionnaires were completed every 3 months. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess mortality rates. The primary end point was OS. Secondary end points included PFS, the percentage of patients with PFS at 6 months, time to progression, 1-year survival rate, QOL, and radiologic response. All end points were evaluated using intention-to-treat analysis.

The trial did not reach its primary end point of improved survival compared with active medical therapy (see Table 6). With a median follow-up of 39 months, 93% of patients had died. There was not a statistically significant difference in survival rates at 1, 2, and 3 years between groups. Patients in the TTF group did not, however, suffer the typical systemic side effects of chemotherapy. The most common adverse event in the TTF group was grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids and did not require treatment breaks. Control participants experienced grade 2, 3, or 4 events by organ system related to the pharmacologic activity of chemotherapy agents used. Hematologic events of

grade 2 or greater were observed in 17% of chemotherapy patients compared with 3% of TTF patients. Gastrointestinal disorders of grade 2 or greater were identified in 17% of chemotherapy patients compared with 4% of TTF patients. Severe (grades 3-4) hematologic and gastrointestinal toxicity was observed in 7% of chemotherapy controls compared with 1% of the TTF group.

Longitudinal QOL data, available in 63 (27%) participants, showed no meaningful differences between groups for the domains of global health and social functioning. However, cognitive and emotional functioning domains favored TTF therapy. Symptom scale analysis was by treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration.

The trial had a number of limitations (see Tables 7 and 8), that included lack of blinding and high loss to follow-up. Discontinuation of TTF therapy occurred in 22% of patients due to noncompliance or inability to handle the device, usually within the first few days. In the control group, 21 (18%) patients did not return to the treatment site, and details on disease progression and toxicity were not available. Longitudinal QOL could be analyzed only for 27% of patients who remained on study therapy for 3 months. The trial was designed as a superiority trial and did not provide adequate evidence of noninferiority.

Table 6. Summary of Key Randomized Controlled Trial Results for Recurrent or Progressive Glioblastoma

| Study; Trial | LTFU, n (%) | Median OS, mo | Progression-Free Survival | | Overall Survival (95% CI, %) | | |
|-----------------------------------------|-------------|---------------------|---------------------------|------------------------------|------------------------------|-------------|------------|
| | | | Median, mo | Rate at 6 Months (95% CI), % | 1 Year | 2 Years | 3 Years |
| Stupp et al (2012) ⁴ ; EF-11 | | | | | | | |
| TTF | 23 (22) | 6.6 | 2.2 | 21.4 (13.5 to 29.3) | 20 | 8 (4 to 13) | 4 (1 to 8) |
| PCC | 12 (18) | 6.0 | 2.1 | 15.1 (7.8 to 22.3) | 20 | 5 (3 to 10) | 1 (0 to 3) |
| HR (95% CI) | | 0.86 (0.66 to 1.12) | 0.81 (0.60 to 1.09) | | | | |
| P value | | 0.27 | 0.16 | 0.13 | | | |

CI: confidence interval; HR: hazard ratio; LTFU: loss to follow-up; PCC: physician's choice chemotherapy; TTF: tumor treating fields.

Table 7. Relevance Gaps

| Study | Population ^a | Intervention ^b | Comparator ^c | Outcomes ^d | Follow-Up ^e |
|-----------------------------------------|-------------------------|---------------------------|------------------------------------|-----------------------|------------------------|
| Stupp et al (2012) ⁴ ; EF-11 | | | 2. Physician's choice chemotherapy | | |

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Gaps

| Study; Trial | Allocation ^a | Blinding ^b | Selective Reporting ^d | Data Completeness ^e | Power ^d | Statistical ^f |
|-----------------------------------------|-------------------------|-----------------------|----------------------------------|------------------------------------------------------------|--------------------|--------------------------|
| Stupp et al (2012) ⁴ ; EF-11 | | 1. Not blinded to | | 1. 78% of TTF group completed only 1 cycle of therapy, 18% | | 1. Not designed as a |

| Study; Trial | Allocation ^a | Blinding ^b | Selective Reporting ^d | Data Completeness ^e | Power ^d | Statistical ^f |
|--------------|-------------------------|-----------------------|----------------------------------|---------------------------------------------------------------------------------------------------|--------------------|--------------------------|
| | | treatment assignment | | of control group lost to follow-up 1. Longitudinal QOL data were available for 27% of patients | | noninferiority trial |

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

QOL: quality of life.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Nonrandomized Comparative Studies

Kesari et al (2017) conducted a post hoc analysis of the EF-14 trial (see Stupp et al [2017] above) to evaluate the efficacy of TTF in patients who had the first recurrence.¹³ Some patients in the temozolomide alone group crossed over to receive TTF plus chemotherapy after the first recurrence, resulting in 144 patients who received TTF fields plus chemotherapy and 60 patients who received chemotherapy alone for recurrent GBM (see Table 9). Patient characteristics and second-line treatments were well-balanced between the groups, with bevacizumab the most common second-line therapy. The median OS in patients treated with systemic therapy alone was 9.2 months (see Table 10). In comparison, the group of patients who received TTF therapy in addition to systemic therapy had a median OS of 11.8 months (p=0.043).

A registry study published Mrugala et al (2014) assessed OS data from patients who received NovoTTF therapy in a real-world, clinical practice setting (see Table 9).¹⁴ Concurrent treatment was not captured in the registry, and it is possible that some patients received combination therapy. Median OS in the PRiDe clinical practice dataset (9.6 mo) was reported as superior to that attained in the EF-11 pivotal trial (6.6 mo, p<0.001) (see Table 10). More patients in the PRiDe registry were treated for first recurrence (33% vs 9%), and more had received bevacizumab as prior therapy (55% vs 19%). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

Table 9. Characteristics of Key Nonrandomized Trial Results

| Study | Study Type | Country | Dates | Participants | TTF | Controls | FU |
|------------------------------------|-------------------------|---------------------------------|-----------|-------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------|---------|
| Kesari et al (2017) ¹³ | EF-14 post hoc analysis | U.S., E.U., South Korea, Israel | 2009-2016 | 204 patients with first recurrence in the EF-14 trial | 144 patients treated with TTF plus second-line chemotherapy | 60 patients treated with second-line chemotherapy | 12.6 mo |
| Mrugala et al (2014) ¹⁴ | Registry | U.S. (91 centers) | 2011-2013 | 457 patients with recurrent GBM | Patient Registry Dataset (PRiDe) | EF-11 | |

FU: follow-up; GBM: glioblastoma; TTF: tumor treating fields.

Table 10. Summary of Key Nonrandomized Trial Results

| Study | Median OS, mo | Median OS With Bevacizumab, mo | | |
|------------------------------------------------|---------------------|--------------------------------|---------------------|---------------------|
| Kesari et al (2017)¹³; EF-14 | | | | |
| TTF plus chemotherapy | 11.8 | 11.8 | | |
| Chemotherapy alone | 9.2 | 9.0 | | |
| Hazard ratio (95% CI) | 0.70 (0.48 to 1.00) | 0.61 (0.37 to 0.99) | | |
| P value | 0.049 | 0.043 | | |
| | | | 1-Year OS, % | 2-Year OS, % |
| Mrugala et al (2014)¹⁴ | | | | |
| PRIDE Registry | 9.6 | 44 | | 30 |
| EF-11 | 6.6 | 20 | | 9 |
| Hazard ratio (95% CI) | 0.66 (0.05 to 0.86) | | | |
| P value | <0.001 | | | |

CI: confidence interval; OS: overall survival; TTF: tumor treating fields.

Post hoc analyses of the EF-11 pivotal trial have been reported. Wong et al (2014) published a subgroup analysis to determine characteristics of responders and nonresponders in the active treatment and active treatment control.¹⁵ They found that responders had a lower grade of histology and lower daily dexamethasone use than nonresponders. A second post hoc analysis by Kanner et al (2014) of the EF-11 pivotal trial data was performed to evaluate OS among patients who finished at least 1 complete course of TTF or chemotherapy.¹⁶ The investigators reported that median OS was 7.7 months in the TTF group compared with 5.9 months in the chemotherapy group ($p=0.009$). These post hoc analyses are considered to be hypothesis-generating.

Section Summary: TTF Therapy as an Adjunct or Alternative to Chemotherapy for Progressive or Recurrent GBM

The single RCT for TTF as an alternative to chemotherapy reported that outcomes following TTF therapy were similar to outcomes following standard chemotherapy. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. The noninferiority of TTF compared with chemotherapy might be considered a sufficient health benefit, if TTF reduced treatment toxicity. However, because the trial was not designed as a noninferiority trial no inferences of noninferiority compared with chemotherapy can be made. Physician's choice therapy during the trial was heterogenous, although analysis indicated that survival was not affected by choice of chemotherapy. More patients in the TTF group than in the control group did not complete the treatment course. The number of patients who contributed QOL data was approximately one-quarter of total enrollment, and the self-reported QOL indicators might have been subject to bias due to the lack of blinding.

A nonrandomized post hoc evaluation of the EF-14 trial suggests that TTF may improve survival when combined with chemotherapy for recurrent GBM. This analysis should be considered hypothesis-generating, and further study in high-quality RCTs is needed.

Summary of Evidence

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes an RCT. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (i.e., temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests from Blue Cross Blue Shield Association, input was received from 3 physician specialty societies (one of which provided 6 responses and 2 of which provided 1 response each) and 1 academic medical center (total of 9 individual responses) in 2016. There was majority support, but not consensus, for the use of tumor treatment fields therapy as an adjunct to maintenance treatment following initial therapy for glioblastoma multiforme. There was mixed support for the use of tumor treatment fields as an alternative to chemotherapy in advanced or recurrent glioblastoma multiforme.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2018) include recommendations for the treatment of glioblastoma (see Table 11).³ For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate O⁶-methylguanine-DNA methyltransferase promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric field therapy is a category 1 recommendation. Alternating electric currents therapy is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a category 2B recommendation.

Table 11. Guidelines for Adjuvant Treatment of Glioblastoma, by Age and Performance Status

| Age, y | KPS Score, % | Treatment Options | Category |
|--------|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| ≤70 | ≥60 | <ul style="list-style-type: none"> Standard RT plus concurrent and adjuvant temozolomide plus TTF Standard RT plus concurrent and adjuvant temozolomide | 1 |
| ≤70 | <60 | <ul style="list-style-type: none"> Hypofractionated RT with/without concurrent or adjuvant temozolomide Temozolomide Palliative/best supportive care | 2A |
| >70 | ≥60 | <ul style="list-style-type: none"> Hypofractionated RT plus concurrent and adjuvant temozolomide Standard RT plus concurrent and adjuvant temozolomide plus TTF Temozolomide alone Hypofractionated brain RT alone | 1 |
| >70 | <60 | <ul style="list-style-type: none"> Hypofractionated brain RT alone Temozolomide alone | 2A |

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| Age, y | KPS Score, % | Treatment Options | Category |
|--------|--------------|-----------------------------------|----------|
| | | • Palliative/best supportive care | |

KPS: Karnofsky Performance Status; RT: radiotherapy; TTF: tumor treating fields.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 12. Of particular note are the phase 3 trials evaluating TTF therapy in non-small-cell lung cancer and pancreatic cancer. TTF therapy is an active area of research for mechanisms underlying its effects on cancer cells.

Table 12. Summary of Key Trials

| NCTNo. | Trial Name | Planned Enrollment | Completion Date |
|--------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Ongoing | | | |
| NCT01971281 ^a | A Phase II Study of TTFs (150 kHz) Concomitant With Gemcitabine and TTFs Concomitant With Gemcitabine Plus Nab-paclitaxel for Front-line Therapy of Advanced Pancreatic Adenocarcinoma | 40 | Dec 2017 (ongoing) |
| NCT01894061 ^a | A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma | 40 | Dec 2018 |
| NCT02663271 ^a | A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the Combination of TTFs and Pulsed Bevacizumab Treatment in Patients With Bevacizumab-refractory Recurrent Glioblastoma | 18 | Mar 2019 |
| NCT02831959 ^a | Pivotal, Open-label, Randomized Study of Radiosurgery With or Without Tumor Treating Fields (TTFs) (150kHz) for 1-10 Brain Metastases From Non-small Cell Lung Cancer (NSCLC) (METIS) | 270 | Jul 2019 |
| NCT02973789 ^a | LUNAR: Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFs) Concurrent With Standard of Care Therapies for Treatment of Stage 4 Non-small Cell Lung Cancer (NSCLC) Following Platinum Failure | 534 | Dec 2021 |
| NCT02743078 ^a | Phase II Trial Of Optune® Plus Bevacizumab In Bevacizumab-Refractory Recurrent Glioblastoma | 85 | Aug 2022 |
| NCT03377491 ^a | EF-27 Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFs, 150kHz) Concomitant With Gemcitabine and Nab-paclitaxel for Front-line Treatment of Locally-advanced Pancreatic Adenocarcinoma (PANOVA-3) | 556 | Dec 2022 |

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

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|------------------------------------------|
| Documentation for Clinical Review |
|------------------------------------------|

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
 - Clinical findings (i.e., pertinent symptoms and duration)
 - Karnofsky Performance Score
 - Past and present diagnostic testing and results

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- o Previous treatment plan and response
- o Tumor type and description
- o Documentation of the patient's understanding on the use of the device
- Radiology report(s) and interpretation (i.e., MRI, CT scan, PET)

Post Service

- Results/reports of test performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

| Type | Code | Description |
|------------------|-------|-------------------------------------------------------------------------------------------------------------|
| CPT® | None | |
| HCPCS | A4555 | Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only |
| | E0766 | Electrical stimulation device used for cancer treatment, includes all accessories, any type |
| ICD-10 Procedure | None | |

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

| Effective Date | Action | Reason |
|----------------|------------------------------------------------------------------------------------------------------------------|--------------------------|
| 10/31/2014 | BCBSA Medical Policy adoption | Medical Policy Committee |
| 05/01/2016 | Policy revision without position change | Medical Policy Committee |
| 10/01/2016 | Policy revision without position change | Medical Policy Committee |
| 09/01/2017 | Policy revision without position change | Medical Policy Committee |
| 11/01/2018 | Policy title change from Tumor Treatment Fields Therapy for Glioblastoma Policy revision with position change | Medical Policy Committee |

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/ Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance

with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guide lines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Medical Policy Reference Manual
Medical Policy

2.03.014 Electric Tumor Treatment Fields

Original MPC Approval: 04/05/2013

Last Review: 03/19/2018

Last Revision: 05/21/2018

Description

Glioblastoma multiforme (GBM) is the most common malignant primary intracranial tumor, with a median survival of only 10-14 months. Only 3% to 5% of patients survive more than 3 years. Recurrence is extremely common, which further decreases survival to 5-7 months. GBM is an aggressive tumor that presents treatment challenges owing to the resistance of the tumor cells to conventional therapies and the susceptibility of the brain to damage.

Electric tumor treatment fields (TTF) are low-intensity, intermediate frequency (100-200 kHz) alternating electric fields currently being explored as a possible method of improving survival in patients with GBM. The device consists of a portable electric field generator, a pair of electrodes, and accessories. The electrodes are placed on the patient's shaved scalp and current is applied at the prescribed frequency. The belief is that alternating electrical fields disrupt the rapidly dividing cancer cells, dislocating intracellular structures and leading to tumor cell death. Healthy brain tissue is not appreciably affected by the electrical current.

Policy

Electric tumor treating fields (TTF) is considered **medically necessary** for the treatment of histologically-confirmed glioblastoma (GBM) in patients 18 years of age and older.

Electric tumor treating fields (TTF) is considered **medically necessary** for patients that have completed debulking surgery or biopsy.

Electric tumor treating fields (TTF) is considered **medically necessary** for patients that have completed chemotherapy therapy and radiation therapy.

Electric tumor treating fields (TTF) is considered **medically necessary** when used concurrent with temozolomide (TMZ) for the treatment of GBM.

Electric tumor treating fields (TTF) is considered **experimental / investigational** for the treatment of any conditions not outlined above.

Policy Guidelines

1. The technology must have final approval from the appropriate government regulatory bodies;

The NovoTTF-100A system (Novocure, Ltd.) received a premarket approval (PMA) from the FDA in April 2011. According to the FDA approval document, "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with histologically confirmed glioblastoma multiforme (GBM), following histologically- or radiologically-confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted."

2. The scientific evidence must permit conclusions concerning the effect on health outcomes:

Pilot-level studies published since 2007 have shown mixed results. Overall when the primary end-point is taken to cancer survival the TTF treatment is similar to active chemotherapy, but quality of life analysis tends to favor the TTF treatment.

3. The technology must improve the net health outcome:

TTF therapy is still considered a novel treatment method, but with a high safety profile. The published evidence is not sufficient to determine net health outcomes.

4. The technology must be as effective as any established alternatives:

In terms of cancer survival, the evidence has not established that TTF treatment is at least as effective as the standard protocol.

5. The improvement must be attainable outside the investigational settings:

It is not known whether improvement can be expected outside of the investigational setting.

Update 2015:

A search of the peer-reviewed literature was performed for the period of March 2013 through October 2015. The NovoTTF-100A system's name was changed to Optune on September 28, 2014, based on a supplemental approval to the original PMA from the FDA. The newly approved, expanded FDA indications for the Optune is for treatment of adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune with temozolomide is intended for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

Electric tumor treatment fields for the treatment of GBM and other solid tumors continue to be evaluated in clinical trials. The policy statement is unchanged.

Update 2018:

A search of the peer-reviewed literature was performed for the period of November 2015 through January 2018. In 2015, Stupp et al published results of a randomized controlled trial (RCT) that evaluated both safety and efficacy of tumor-treating field (TTF) used in combination with temozolomide maintenance treatment after chemoradiation therapy for patients with glioblastoma multiforme (GBM). 695 patients were randomized in a 2:1 fashion to either receive maintenance treatment with TTF with temozolomide (TMZ) (n=466) or TMZ alone (n=229). Study eligibility required patients to be 18 years or older, have a histologically confirmed supratentorial glioblastoma, be progression-free after having undergone maximal safe debulking surgery when feasible or biopsy, and have completed standard concomitant chemoradiotherapy with TMZ. The median time from diagnosis to randomization was 3.8 months in both groups and patients were not blinded due to ethical concerns. TTF was delivered continuously (> 18 hours/day) via 4 transducers placed on the shaved scalp and TMZ (150-200 mg/m²/d) was given for 5 days of each 28-day cycle. Transducer array layouts were determined using the NvoTAL mapping software system for TTF fields to optimize field intensity within the treated tumor. A planned interim analysis was to be conducted on the first 315 patients at 18 months follow-up. The primary study endpoint was progression-free survival (PFS) in the intent-to treat populations (with a significance threshold of p<0.01) with overall survival (OS) in the per-protocol population (n = 280) as a powered secondary end point (significance threshold of .006). A total of 695 4 – DME85 patients were enrolled across 83 centers; however, the trial was terminated as it met its efficacy endpoints at interim analysis (median 38 months, 315 patients). The interim analysis included the planned 315 subjects, with 210 in the TTF/TMZ group and 105 in the TMZ only group. The analysis was conducted at a median 38 months follow-up (range, 18-60 months). Prespecified per-protocol median PFS in the TTF/TMZ group was 7.1 months (95% CI, 5.9- 8.2 months) compared to 4 months (95% CI, 3.3-5.2 months) in the TMZ only group (hazard ratio (HR), 0.62 [98.7% CI, 0.43-0.89]; P = .001). The median OS in the per-protocol population was statistically improved in the TTF/TMZ group (20.5 months; 95% CI, 16.7-25.0 months) compared to the TMZ only group (15.6 months; 95% CI, 13.3-19.1 months; HR, 0.64 [99.4% CI, 0.42-0.98]; P = .004). An additional analysis of the intention-to-treat population demonstrated and OS of 19.6 months (95% CI, 16.6-24.4 months) in the TTF/TMZ group compared to 16.6 months (95% CI, 13.6- 19.2 months) in the TMZ only group (HR, 0.74 [95% CI, 0.56-0.98]; stratified log-rank p = .03). Forty-three percent of patients in the TTF/TMZ group were alive at 2-year follow-up, compared to 29% in the TMZ only group (p = .006).

The results of this study demonstrate an approximate three-month improvement of PFS and five-month improvement of OS when TTF therapy is used concurrently with TMZ in patients with newly diagnosed GBM.

Benefit Applications

Electric tumor treatment fields (TTF) services must be preauthorized for HMO members only. Providers should submit preauthorization requests online at <https://provider.carefirst.com> or call 1-866-773-2884 (1-866-PRE-AUTH).

Check the member's contract for benefits.

NOTE: For FEP business, check the member's contract for benefits.

References

The following were among the resources reviewed and considered in developing this policy. By reviewing and considering the resources, CareFirst does not in any way endorse the contents thereof nor assume any liability or responsibility in connection therewith. The opinions and conclusions of the authors of these resources are their own, and may or may not be in agreement with those of CareFirst.

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This policy statement relates only to the services or supplies described herein. Coverage will vary from contract to contract and by line of business and should be verified before applying the terms of the policy.

Clinical Policy: Electric Tumor Treating Fields (Optune)

Reference Number: CP.MP.145

Last Review Date: 03/18

Coding Implications

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Electric tumor treating fields (TTF), also known as alternating electric field therapy, are used for the treatment of glioblastoma, and are delivered by Optune® (NovoCure™), a portable medical device that generates low-intensity electric fields termed Tumor Treating Fields. TTF are believed to disrupt the rapid cell division exhibited by cancer cells, with the alternating electrical fields applied to the brain through electrodes placed on the scalp. The device is worn by the patient throughout the day and attached to the head by electrodes which creates a low intensity, alternating electric field within the tumor that exerts physical forces on electrically charged cellular components, preventing the normal mitotic process and causing cancer cell death prior to division.

Policy/Criteria

- I. It is the policy of health plans affiliated with Centene Corporation® that TTF therapy is **medically necessary** for the following indication:
 - A. New diagnosis of glioblastoma, histologically confirmed, and all of the following:
 1. Glioblastoma is in the supratentorial region;
 2. Member has good performance status, as defined by a Karnofsky Performance Status rating of ≥ 60 ;
 3. Alternating electric field therapy will be delivered in conjunction with temozolomide after standard surgical and radiation therapies have been completed.
 - B. Recurrent glioblastoma, histologically- or radiologically- confirmed and all of the following:
 1. Glioblastoma is in the supratentorial region;
 2. Alternating electric field therapy will be used as a monotherapy, after standard treatment with surgery, radiation, and chemotherapy.
- II. It is the policy of health plans affiliated with Centene Corporation® that TTF therapy is **investigational and not medically necessary** for all other indications.
- III. It is the policy of health plans affiliated with Centene Corporation® that computer mapping software (NovoTal™) for planning TTF therapy is **investigational and not medically necessary** for all indications, as there is insufficient evidence to establish the efficacy of these products in the long-term outcomes of patients receiving TTF therapy.

Background

Optune Product Description¹

Optune, formerly NovoTTF-100A produces alternating electrical fields within the human body that disrupt the rapid cell division exhibited by cancer cells, with the alternating electrical fields applied to the brain through transducer arrays placed on the scalp. Electric TTF alter the tumor cell polarity at an intermediate frequency (on the order of 100-300 kHz). The frequency used for

a particular treatment is specific to the cell type being treated (e.g., 200kHz for GBM). In contrast, the TTF have not been shown to have an effect on cells that are not undergoing division. Since most normal adult brain cells proliferate very slowly, if at all, they are hypothesized to be little affected by the TTF. Testing demonstrates no differences between treated and control animals in histology of the major internal organs (including the brain), blood examination, cardiac rhythm, body temperature, or in animal behavior. In addition, because the fields alternate so rapidly, they have no effect on normal quiescent cells nor do they stimulate nerves and muscles. It is noted that, because TTF are only applied to the brain, they have no effect on rapidly proliferating cells in the rest of the body. The intensities of the electric fields within the tissues are very small and do not result in any meaningful increase in tissue temperature. Thus, TTF application has the advantage of being highly selective and is not expected to be associated with significant toxicity.

Position Statement

Guidelines from the National Comprehensive Cancer Network (NCCN) on central nervous system cancers, recommend alternating electrical fields therapy as a treatment option for newly diagnosed glioblastoma (2A- uniform consensus, based on low-quality evidence). The NCCN guidelines state TTF is recommended “for patients with good performance status and either methylated or unmethylated/indeterminate MGMT promoter status,” in conjunction with standard brain radiation therapy plus concurrent temozolomide and adjuvant temozolomide.² For recurrent glioblastoma, NCCN gives alternating electrical field therapy a 2B rating (consensus based on low-quality evidence).²

Evidence for Optune

Initial FDA approval for recurrent glioblastoma was based on Stupp et al.’s 2012³ phase III clinical trial that randomized 237 patients to chemotherapy-free treatment of NovoTTF (20-24h/day) versus active chemotherapy in the treatment of patients with recurrent glioblastoma⁵. Primary end-point was improvement of overall survival. Patients were randomized to TTF alone or active chemotherapy control. Responses were more common in the TTF arm (14% versus 9.6%, p=0.19) and TTF-related adverse events were mild. Quality of life analyses favored TTF therapy in most domains. The investigators concluded that no improvement in overall survival was demonstrated. However, efficacy and activity with this chemotherapy-free treatment device appears comparable to chemotherapy regimens that are commonly used for recurrent glioblastoma. Toxicity and quality of life measures favored TTF.

The FDA based its approval⁴ of the newly diagnosed glioblastoma indication of the Optune device on results from a 2015 clinical trial by Stupp et al.⁵. The EF-14 trial included 695 patients newly diagnosed with GB, and compared those who used Optune with temozolomide to those receiving temozolomide alone. Patients who used the device along with temozolomide lived, on average, about seven months with no disease progression compared to four months for those who had the drug alone. The Optune plus temozolomide group survived for an average of 19.4 months after starting treatment compared to 16.6 months for those who were treated with only temozolomide⁵. One critique of this study is that the study was terminated at the pre-planned intermediate analysis due to success of the TTF treatment. With the newly diagnosed glioblastoma indication, Optune can be used for GBM before the disease progresses. For newly

diagnosed GBM, Optune is not intended to be used as a substitute for standard treatments, but rather as an adjunct therapy, and should not be used without a physician's supervision.

Hayes conducted a review of the available literature on TTF, noting that overall the body of evidence was of fair to very poor quality, although it was consistently positive.⁶ Hayes found the evidence to be stronger for the use of TTF for recurrent disease as opposed to newly diagnosed disease, as there were more supportive studies for recurrent disease at the time of publication (2 vs. 6). Out of the 10 studies they reviewed, pertaining to the use of TTF in patients with GBM and select other cancers, two were of fair quality, and the other eight ranged from poor quality to very poor quality. The two fair quality trials were those conducted by Stupp et al. in 2012⁵ and 2015⁴, although these were noted to have limitations such as lack of a sham intervention and significant loss to follow up (22% and 20%, respectively)⁶.

A post-hoc analysis of Stupp et al.'s E-14 trial of TTF plus temozolomide versus temozolomide alone in newly diagnosed glioblastoma compared the efficacy of TTF plus physician's choice of chemotherapy versus chemotherapy alone after first recurrence⁷. Median overall survival in the TTF plus chemotherapy was 11.8 months versus 9.2 months for the chemotherapy only group ($p=.049$)⁷. TTF demonstrated low toxicity, consistent with previous studies. Limitations of this analysis are its post-hoc nature, as well as the crossover of 13 patients from the temozolomide only group to the TTF plus chemo group after approval and commercial availability of TTF for recurrent GBM⁷.

Vymazal et al.⁸ analyzed the response patterns in individuals who exhibited an objective response to TTF in two previous studies in order to evaluate the baseline characteristics of those individuals who responded and to evaluate the relationship between compliance with use and efficacy outcomes. The analysis was completed on one pilot study ($n=10$) and a phase III trial ($n=237$) in which TTF was compared to standard chemotherapy. Between both studies, TTF was administered as monotherapy in 130 individuals. Across both trials, there was a 15% response rate (16/110 with a 4% complete response rate)⁸. There were no significant differences in baseline characteristics between the responder and nonresponder groups. In those in which a response was noted, there was frequently a delayed response; the tumor would initially continue to grow before responding to treatment. Analysis supported that an increase in compliance was associated with better treatment response and longer OS. The extent of treatment response in those who exhibited a response was dependent on compliance ($p<0.001$)⁸.

Although Optune is promising for the treatment of newly diagnosed glioblastoma, there is insufficient evidence to promote it as standard of care at this time. Evidence is stronger for recurrent glioblastoma which has been previously treated with radiation, surgery and chemotherapy.

NovoTal

The NovoTal system (Novocure) is a computer software planning tool that helps direct placement of transducer arrays for TTF therapy. Few studies have evaluated outcomes of TTF planned by physicians with and without the use of NovoTal, and these are limited to a case series, physician use study, and two review articles. Additionally, many of the authors reported ties to Novocure.

CLINICAL POLICY
Electric Tumor Treating fields

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

| HCPSC Codes | Description |
|-------------|-------------------------------------------------------------------------------------------------------------|
| A4555 | Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only |
| E0766 | Electrical stimulation device used for cancer treatment, includes all accessories, any type |

ICD-10-CM Diagnosis Codes that Support Coverage Criteria

| ICD-10-CM Code | Description |
|----------------|----------------------------------------------------------------------------------------|
| C71.0 - C71.9 | Malignant neoplasm of brain [supratentorial glioblastomas (WHO grade IV astrocytomas)] |

| Reviews, Revisions, and Approvals | Date | Approval Date |
|-----------------------------------------------------------------------|-------|---------------|
| Policy adopted from Health Net Electric Tumor Treating fields policy. | 04/17 | 05/17 |
| Added new diagnosis of glioblastoma as medically necessary. | 06/17 | 06/17 |
| References reviewed and updated. Background updated. Codes reviewed. | 03/18 | 03/18 |

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

CLINICAL POLICY
Electric Tumor Treating fields

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

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Medical Coverage Policy



Effective Date..... 7/15/2018
Next Review Date..... 3/15/2019
Coverage Policy Number 0504

Omnibus Codes

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Related Coverage Resources

Computerized Electrocardiograph (ECG) Analysis
Deep Brain and Motor Cortex and Responsive Cortical Stimulation
Nerve Conduction, Neuromuscular Junction, and Electromyography Testing
Serological Testing for Inflammatory Bowel Disease
Somatosensory Evoked Potentials

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

High Resolution Anoscopy (CPT Codes 46601, 46607)

High resolution anoscopy (HRA) is considered medically necessary for diagnosis of EITHER of the following:

- suspicious anal lesion, including high-grade suspicious intraepithelial lesion (HSIL)
- anal dysplasia found in prior cytology/biopsy

HRA for any other indication is considered experimental, investigational and unproven.

Whole Body and Selective Head Hypothermia (CPT code 99184)

Whole body or selective head therapeutic hypothermia in a neonate ≤ 28 days of age is considered medically necessary for the treatment of moderate or severe hypoxic ischemic encephalopathy.

Whole body or selective head therapeutic hypothermia in a neonate ≤ 28 days of age for any other indication is considered experimental, investigational or unproven.

Tumor Treatment Fields (TTF) Therapy (HCPCS Codes A4555, E0766, 64999)

TTF therapy (i.e., Optune™) is considered medically necessary for individual 22 years of age or older with presence of histologically-confirmed glioblastoma multiforme (GBM) when EITHER of the following criteria are met:

- with confirmed recurrence after receiving chemotherapy and the device is being used as a monotherapy
- for adjuvant therapy with temozolomide

TTF (i.e., Optune™) for any other indication is considered experimental, investigational or unproven.

The use of treatment planning software (i.e., NovoTAL) (CPT code 64999) for use with tumor treatment fields for any indication, is considered experimental, investigational or unproven.

Insertion of Ocular Telescope Prosthesis Including Crystalline Lens (CPT Code 0308T, HCPCS Code C1840)

Intraocular telescope (Implantable Miniature Telescope [IMT]) is considered as medically necessary for an individual 65 years of age or older when ALL of the following criteria are met:

- with stable severe to profound vision impairment (best corrected distance visual acuity 20/160 to 20/800) caused by bilateral central scotomas associated with end-stage age-related macular degeneration (AMD)
- has retinal findings of geographic atrophy or disciform scar with foveal involvement, as determined by fluorescein angiography
- has evidence of visually significant cataract (\geq grade 2)
- agrees to undergo pre-surgery training and assessment (two to four visits) with low vision specialists (e.g., optometrist or occupational therapist) in the use of an external telescope
- achieve at least a 5-letter improvement on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart with an external telescope on the eye scheduled for surgery
- have adequate peripheral vision in the eye not scheduled for surgery
- agree to participate in postoperative visual training with a low vision specialist

EXPERIMENTAL, INVESTIGATIONAL OR UNPROVEN

MarginProbe® (CPT Code 19499)

MarginProbe (CPT code 19499) for any indication is considered experimental, investigational or unproven.

Conjunctival Incision with Posterior Extrasccleral Placement of a Pharmacological Agent (CPT Code 68399)

Conjunctival incision with posterior extrasccleral placement of a pharmacological agent (CPT Code 68399) for any indication is considered experimental, investigational or unproven.

Multivariate Analysis of Patient Specific Findings with Quantifiable Computer Probability Assessment (CPT Code 99199)

Multivariate analysis of patient specific findings with quantifiable computer probability assessment (CPT code 99199) is considered experimental, investigational or unproven.

Suprachoroidal Delivery of Pharmacological Agent (CPT Code 67299)

Suprachoroidal delivery of pharmacological agent (CPT code 67299) is considered experimental, investigational or unproven.

OTHER EXPERIMENTAL, INVESTIGATIONAL OR UNPROVEN SERVICES

Each of the following services for any indication is considered experimental, investigational or unproven:

| CPT® Codes | Description | Comment |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| <u>32994</u> | Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging guidance when performed, unilateral; cryoablation | |
| <u>33340</u> | Percutaneous transcatheter closure of the left atrial appendage with endocardial implant, including fluoroscopy, transseptal puncture, catheter placement(s), left atrial angiography, left atrial appendage angiography, when performed, and radiological supervision and interpretation | |
| <u>34806</u> | Transcatheter placement of wireless physiologic sensor in aneurysmal sac during endovascular repair, including radiological supervision and interpretation, instrument calibration, and collection of pressure data (List separately in addition to code for primary procedure) | |
| <u>34839</u> | Physician planning of a patient-specific fenestrated visceral aortic endograft requiring a minimum of 90 minutes of physician time | |
| <u>34841</u> | Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including one visceral artery endoprosthesis (superior mesenteric, celiac or renal artery) | |
| <u>34842</u> | Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including two visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s]) | |
| <u>34843</u> | Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including three visceral artery | |

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| | endoprostheses (superior mesenteric, celiac and/or renal artery[s]) | |
| <u>34844</u> | Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including four or more visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s]) | |
| <u>34845</u> | Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including one visceral artery endoprosthesis (superior mesenteric, celiac or renal artery) | |
| <u>34846</u> | Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including two visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s]) | |
| <u>34847</u> | Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including three visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s]) | |
| <u>34848</u> | Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including four or more visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s]) | |
| <u>46999</u> | Unlisted procedure, anus | Considered Experimental/Investigational/Unproven when used to report transanal radiofrequency therapy for fecal Incontinence (e.g., SECCA procedure) |
| <u>58674</u> | Laparoscopy, surgical, ablation of uterine fibroid(s) including intraoperative ultrasound guidance and monitoring, radiofrequency | |
| <u>64999</u> | Unlisted procedure, nervous system | Considered Experimental/Investigational/ |

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| | | Unproven when used to report implantation of trial or permanent electrode arrays or pulse generators for peripheral subcutaneous field stimulation |
| <u>83993</u> | Calprotectin, fecal | |
| <u>84999</u> | Unlisted chemistry procedure | Considered Experimental/Investigational/Unproven when used to report Holotranscobalamin, quantitative (Holtranscobalamin Testing) |
| <u>88749</u> | Unlisted in vivo (eg, transcutaneous) laboratory service | Considered Experimental/Investigational/Unproven when used to report skin advanced glycation endproducts measurement by multi-wavelength fluorescent spectroscopy |
| <u>91112</u> | Gastrointestinal transit and pressure measurement, stomach through colon, wireless capsule, with interpretation and report | |
| <u>91299</u> | Unlisted diagnostic gastroenterology procedure | Considered Experimental/Investigational/Unproven when used to report 13C-Spirulina Gastric Emptying Breath Test (GEBT) |
| <u>92978</u> | Endoluminal imaging of coronary vessel or graft using intravascular (IVUS) or optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; initial vessel (List separately in addition to code for primary procedure) | Considered Experimental/Investigational/Unproven when used to report CPT code 92978 using endoluminal imaging of coronary vessel or graft using optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; initial vessel |
| <u>92979</u> | Endoluminal imaging of coronary vessel or graft using intravascular (IVUS) or optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; each additional vessel (List separately in addition to code for primary procedure) | Considered Experimental/Investigational/Unproven when used to report CPT code 92979 using endoluminal imaging of coronary vessel or graft using optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; each additional |

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| | | vessel |
| <u>93702</u> | Bioimpedance spectroscopy (BIS), extracellular fluid analysis for lymphedema assessment(s) | |
| <u>93799</u> | Unlisted cardiovascular service or procedure | Considered Experimental/Investigational/ Unproven when used to report acoustic cardiography |
| <u>93982</u> | Noninvasive physiologic study of implanted wireless pressure sensor in aneurysmal sac following endovascular repair, complete study including recording, analysis of pressure and waveform tracings, interpretation and report (Code deleted 12/31/2017) | |
| <u>94799</u> | Unlisted pulmonary service or procedure | Considered Experimental/Investigational/ Unproven when used to report intermittent measurement of wheeze rate for bronchodilator or bronchial challenge diagnostic evaluation |
| <u>95999</u> | Unlisted neurological or neuromuscular diagnostic procedure | Considered Experimental/Investigational/ Unproven when used to report tremor measurement with accelerometer(s) and/or gyroscope(s) |
| <u>99199</u> | Unlisted special service, procedure or report | Considered Experimental/Investigational/ Unproven when used to report near-infrared guidance for vascular access requiring real-time digital visualization of subcutaneous vasculature for evaluation of potential access sites and vessel patency |
| <u>0100T</u> | Placement of a subconjunctival retinal prosthesis receiver and pulse generator, and implantation of intra-ocular retinal electrode array, with vitrectomy | |
| <u>0106T</u> | Quantitative sensory testing (QST), testing and interpretation per extremity; using touch pressure stimuli to assess large diameter sensation | |
| <u>0107T</u> | Quantitative sensory testing (QST), testing and interpretation per extremity; using vibration stimuli to assess large diameter fiber sensation | |
| <u>0108T</u> | Quantitative sensory testing (QST), testing and interpretation per extremity; using cooling stimuli to assess small nerve fiber sensation and hyperalgesia | |
| <u>0109T</u> | Quantitative sensory testing (QST), testing and interpretation per extremity; using heat-pain stimuli to assess small nerve fiber sensation and hyperalgesia | |
| <u>0110T</u> | Quantitative sensory testing (QST), testing and interpretation per extremity; using other stimuli to assess sensation | |
| <u>0174T</u> | Computer aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician | |

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| | review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed concurrent with primary interpretation (List separately in addition to code for primary procedure) | |
| <u>0175T</u> | Computer aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed remote from primary interpretation | |
| <u>0190T</u> | Placement of intraocular radiation source applicator (List separately in addition to primary procedure) | |
| <u>0205T</u> | Intravascular catheter-based coronary vessel or graft spectroscopy (eg, infrared) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation, and report, each vessel (List separately in addition to primary procedure) | |
| <u>0207T</u> | Evacuation of meibomian glands, automated, using heat and intermittent pressure, unilateral | |
| <u>0208T</u> | Pure tone audiometry (threshold), automated; air only | |
| <u>0209T</u> | Pure tone audiometry (threshold), automated; air and bone | |
| <u>0210T</u> | Speech audiometry threshold, automated | |
| <u>0211T</u> | Speech audiometry threshold, automated with speech recognition | |
| <u>0212T</u> | Comprehensive audiometry threshold evaluation and speech recognition (0209T, 0211T combined), automated | |
| <u>0234T</u> | Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; renal artery | |
| <u>0235T</u> | Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; visceral artery (except renal), each vessel | |
| <u>0236T</u> | Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; abdominal aorta | |
| <u>0237T</u> | Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; brachiocephalic trunk and branches, each vessel | |
| <u>0238T</u> | Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; iliac artery, each vessel | |
| <u>0254T</u> | Endovascular repair of iliac artery bifurcation (eg, aneurysm, pseudoaneurysm, arteriovenous malformation, trauma, dissection) using bifurcated endograft from the common iliac artery into both the external and internal iliac artery, including all selective and/or nonselective catheterization(s) required for device placement and all associated radiological supervision and interpretation, unilateral | |
| <u>0255T</u> | Endovascular repair of iliac artery bifurcation (eg, aneurysm, pseudoaneurysm, arteriovenous malformation, trauma) using bifurcated endoprosthesis from the common iliac artery into both the external and internal iliac artery, unilateral; radiological supervision and interpretation (Code deleted 12/31/2017) | |
| <u>0266T</u> | Implantation or replacement of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intraoperative interrogation, programming, and repositioning, when performed) | |

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| <u>0267T</u> | Implantation or replacement of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming and repositioning, when performed) | |
| <u>0268T</u> | Implantation or replacement of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed) | |
| <u>0269T</u> | Revision or removal of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed) | |
| <u>0270T</u> | Revision or removal of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed) | |
| <u>0271T</u> | Revision or removal of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed) | |
| <u>0272T</u> | Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (eg, battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day); | |
| <u>0273T</u> | Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (eg, battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day); with programming | |
| <u>0291T</u> | Intravascular optical coherence tomography (coronary native vessel or graft) during diagnostic evaluation and/or therapeutic intervention, including imaging supervision, interpretation, and report; initial vessel (List separately in addition to primary procedure) (Code deleted 12/31/2016) | |
| <u>0293T</u> | Insertion of left atrial hemodynamic monitor; complete system, includes implanted communication module and pressure sensor lead in left atrium including transseptal access, radiological supervision and interpretation, and associated injection procedures, when performed (Code deleted 12/31/2017) | |
| <u>0294T</u> | Insertion of left atrial hemodynamic monitor; pressure sensor lead at time of insertion of pacing cardioverter-defibrillator pulse generator including radiological supervision and interpretation and associated injection procedures, when performed (List separately in addition to primary procedure) (Code deleted 12/31/2017) | |
| <u>0337T</u> | Endothelial function assessment, using peripheral vascular response to reactive hyperemia, non-invasive (eg, brachial artery ultrasound, peripheral artery tonometry), unilateral or bilateral | |
| <u>0338T</u> | Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; | |

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| | unilateral | |
| <u>0339T</u> | Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; bilateral | |
| <u>0340T</u> | Ablation, pulmonary tumor(s), including pleura or chest wall when involved by tumor extension, percutaneous, cryoablation, unilateral, includes imaging guidance (Code deleted 12/31/2017) | |
| <u>0341T</u> | Quantitative pupillometry with interpretation and report, unilateral or bilateral | |
| <u>0342T</u> | Therapeutic apheresis with selective HDL delipidation and plasma reinfusion | |
| <u>0351T</u> | Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; real-time intraoperative | |
| <u>0352T</u> | Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; interpretation and report, real-time or referred | |
| <u>0353T</u> | Optical coherence tomography of breast, surgical cavity; real-time intraoperative | |
| <u>0354T</u> | Optical coherence tomography of breast, surgical cavity; interpretation and report, real-time or referred | |
| <u>0378T</u> | Visual field assessment, with concurrent real time data analysis and accessible data storage with patient initiated data transmitted to a remote surveillance center for up to 30 days; review and interpretation with report by a physician or other qualified health care professional | |
| <u>0379T</u> | Visual field assessment, with concurrent real time data analysis and accessible data storage with patient initiated data transmitted to a remote surveillance center for up to 30 days; technical support and patient instructions, surveillance, analysis, and transmission of daily and emergent data reports as prescribed by a physician or other qualified health care professional | |
| <u>0380T</u> | Computer-aided animation and analysis of time series retinal images for the monitoring of disease progression, unilateral or bilateral, with interpretation and report | |
| <u>0381T</u> | External heart rate and 3-axis accelerometer data recording up to 14 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional | |
| <u>0382T</u> | External heart rate and 3-axis accelerometer data recording up to 14 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only | |
| <u>0383T</u> | External heart rate and 3-axis accelerometer data recording from 15 to 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional | |
| <u>0384T</u> | External heart rate and 3-axis accelerometer data recording from | |

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| | 15 to 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only | |
| <u>0385T</u> | External heart rate and 3-axis accelerometer data recording more than 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional | |
| <u>0386T</u> | External heart rate and 3-axis accelerometer data recording more than 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only | |
| <u>0397T</u> | Endoscopic retrograde cholangiopancreatography (ERCP), with optical endomicroscopy (List separately in addition to code for primary procedure) | |
| <u>0404T</u> | Transcervical uterine fibroid(s) ablation with ultrasound guidance, radiofrequency | |
| <u>0408T</u> | Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator with transvenous electrodes | |
| <u>0409T</u> | Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator only | |
| <u>0410T</u> | Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; atrial electrode only | |
| <u>0411T</u> | Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; ventricular electrode only | |
| <u>0412T</u> | Removal of permanent cardiac contractility modulation system; pulse generator only | |
| <u>0413T</u> | Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular) | |
| <u>0414T</u> | Removal and replacement of permanent cardiac contractility modulation system pulse generator only | |
| <u>0415T</u> | Repositioning of previously implanted cardiac contractility modulation transvenous electrode, (atrial or ventricular lead) | |
| <u>0416T</u> | Relocation of skin pocket for implanted cardiac contractility modulation pulse generator | |
| <u>0417T</u> | Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, including review and report, implantable cardiac contractility modulation system | |
| <u>0418T</u> | Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter; implantable cardiac contractility modulation system | |
| <u>0465T</u> | Suprachoroidal injection of a pharmacologic agent (does not include supply of medication) | |

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| <u>0472T</u> | Device evaluation, interrogation, and initial programming of intraocular retinal electrode array (eg, retinal prosthesis), in person, with iterative adjustment of the implantable device to test functionality, select optimal permanent programmed values with analysis, including visual training, with review and report by a qualified health care professional | |
| <u>0473T</u> | Device evaluation and interrogation of intraocular retinal electrode array (eg, retinal prosthesis), in person, including reprogramming and visual training, when performed, with review and report by a qualified health care professional | |
| <u>0493T</u> | Near-infrared spectroscopy studies of lower extremity wounds (eg, for oxyhemoglobin measurement) | |

| HCPCS Codes | Description |
|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <u>C1841</u> | Retinal prosthesis, includes all internal and external components |
| <u>C1842</u> | Retinal prosthesis, includes all internal and external components; add-on to C1841 |
| <u>C2624</u> | Implantable wireless pulmonary artery pressure sensor with delivery catheter, including all system components |
| <u>C9741</u> | Right heart catheterization with implantation of wireless pressure sensor in the pulmonary artery, including any type of measurement, angiography, imaging supervision, interpretation, and report |
| <u>E2120</u> | Pulse generator system for tympanic treatment of inner ear endolymphatic fluid |
| <u>G0255</u> | Current perception threshold/sensory nerve conduction test, (sNCT) per limb, any nerve |
| <u>S2103</u> | Adrenal tissue transplant to brain |

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Overview

This Coverage Policy addresses multiple services and procedures.

General Background

Subsections:

Services without Food and Drug Administration (FDA) Approval

Cardiovascular

Pulmonary

Gastroenterology

Neurology

Obstetrics/Gynecology

Ophthalmology

Oncology

Otolaryngology

Other

Services without Food and Drug Administration (FDA) Approval

This policy discusses the safety and effectiveness of certain technologies, services, and procedures, including those represented by some Category III CPT® codes. Category III codes are temporary codes that allow for data collection for these services/procedures.

Additionally, there are certain codes, including mainly Category III codes that represent services which have not yet received Food and Drug Administration (FDA) approval:

| CPT® Codes | Description | Comment |
|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 88749 | Unlisted in vivo (eg, transcutaneous) laboratory service | Considered Experimental/Investigational/Unproven when used to report skin advanced glycation endproducts measurement by multi-wavelength fluorescent spectroscopy |
| 0190T | Placement of intraocular radiation source applicator (List separately in addition to primary procedure) | |
| 0293T | Insertion of left atrial hemodynamic monitor; complete system, includes implanted communication module and pressure sensor lead in left atrium including transeptal access, radiological supervision and interpretation, and associated injection procedures, when performed (Code deleted 12/31/2017) | |
| 0294T | Insertion of left atrial hemodynamic monitor; pressure sensor lead at time of insertion of pacing cardioverter-defibrillator pulse generator including radiological supervision and interpretation and associated injection procedures, when performed (List separately in addition to primary procedure) (Code deleted 12/31/2017) | |
| 0338T | Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; unilateral | |
| 0339T | Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; bilateral | |
| 0342T | Therapeutic apheresis with selective HDL delipidation and plasma reinfusion | |
| 0404T | Transcervical uterine fibroid(s) ablation with ultrasound guidance, radiofrequency | |
| 0408T | Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator with transvenous electrodes | |
| 0409T | Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator only | |
| 0410T | Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; atrial electrode only | |
| 0411T | Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; ventricular electrode only | |

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| 0412T | Removal of permanent cardiac contractility modulation system; pulse generator only | |
| 0413T | Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular) | |
| 0414T | Removal and replacement of permanent cardiac contractility modulation system pulse generator only | |
| 0415T | Repositioning of previously implanted cardiac contractility modulation transvenous electrode, (atrial or ventricular lead) | |
| 0416T | Relocation of skin pocket for implanted cardiac contractility modulation pulse generator | |
| 0417T | Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, including review and report, implantable cardiac contractility modulation system | |
| 0418T | Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter; implantable cardiac contractility modulation system | |

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Cardiovascular

Percutaneous transcatheter closure of the left atrial appendage (Codes 33340)

Minimally invasive procedures for closure of the left atrial appendage (LAA) have been developed for the purpose of prevention of stroke. In an individual with atrial fibrillation (AF); it is a potential source for blood clots to form that lead to stroke. Percutaneous LAA closure devices are a nonpharmacologic alternative to anticoagulation for stroke prevention in AF. It is theorized that the devices may prevent thrombus formation and stroke by occluding the LAA.

The Watchman™ Left Atrial Appendage Closure Device (Boston Scientific, Maple Grove, MN) is a self-expanding nickel-titanium system. Implantation is performed percutaneously with a catheter delivery system, with venous access and trans-septal puncture to enter the left atrium. After implantation of device, patients receive anticoagulation with warfarin or other agents for approximately one to two months. During this acute period of time, anticoagulation may be necessary due to risk of thrombus formation related to altered blood flow around the implant. Patients are monitored with transesophageal echocardiography to assess blood flow and complete LAA closure (LAAC). After this period, patients will receive antiplatelet agents (e.g., aspirin and/or clopidogrel) indefinitely.

Other available devices that have not received FDA approval for the use of LAA closure include:

- The Amplatzer™ Cardiac Plug (St. Jude Medical, Minneapolis, MN) is approved for LAAC in Europe. The device closes off the LAA in a manner similar to the Watchman. The technique for implanting this device is also similar to that of the Watchman™ system.
- The Lariat® Loop Applicator is a suture delivery device that is designed to close a variety of surgical wounds in addition to LAAC. The technical approach differs from that of the Watchman system. The Lariat suture loop ligates the LAA from the epicardial space, with assistance of catheters and balloons in the left atrium.

U.S. Food and Drug Administration (FDA)

The Watchman LAA Closure Technology received FDA premarket approval March 2015. The approval notes that the device is indicated to reduce the risk of thromboembolism from the left atrial appendage (LAA) in patients with non-valvular atrial fibrillation who:

- are at increased risk for stroke and systemic embolism based on CHADS₂ (cardiac failure, hypertension, age ≥ 75 years, diabetes, stroke) or CHA₂DS₂-VASc¹ (congestive heart failure, hypertension, age ≥ 75

years, diabetes, stroke/transient ischemic attack/thromboembolism, vascular disease, aged 65 to 74 years, sex category [female]) scores and are recommended for anticoagulation therapy

- are deemed by their physicians to be suitable for warfarin
- have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin

Other devices that have not received FDA approval for the use of LAA closure include but are not limited to:

- The Amplatzer™ Cardiac Plug (St. Jude Medical, Minneapolis, MN) is approved for LAAC in Europe. The device closes off the LAA in a manner similar to the Watchman. The technique for implanting this device is also similar to that of the Watchman system.
- The Lariat® Loop Applicator (Sentreheart, Palo Alto, CA) is a suture delivery device that is designed to close a variety of surgical wounds in addition to LAAC. The Lariat Loop Applicator device did receive 510(k) marketing clearance from FDA in 2006 as suture delivery device, but does not have FDA approval as a LAA closure device. Its intended use is to facilitate suture placement and knot tying in surgical applications where soft tissues are being approximated or ligated with a pretied polyester suture. The technical approach differs from that of the Watchman system. The Lariat suture loop ligates the LAA from the epicardial space, with assistance of catheters and balloons in the left atrium.
- PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) device (Appriva Medical, Inc., Sunnyvale, CA, USA) is no longer in production.

Literature Review

Saw et al. (2017) reported on a study to evaluate the safety and efficacy of WATCHMAN of 106 patients who underwent WATCHMAN implantation at four major Canadian centers. The indications for left atrial appendage (LAA) closure were CHADS₂ ≥ 1 or CHA₂ DS₂ -VASc ≥ 2, and a contraindication/intolerance to or failure on anticoagulation. Follow-up imaging was typically performed 1-6 months postprocedure. Procedural success was 97.2% (103 of 106): one device embolization (snared percutaneously); one implant failure due to inadequate LAA depth; and, one cardiac perforation requiring surgical repair before WATCHMAN implantation. The composite major safety event-rate was 1.9% (one death and one device embolization). Antithrombotic therapy postimplant included dual antiplatelet therapy in 76 of 103 (73.8%). The mean follow-up was 210±182 days; there were two transient ischemic attacks, with estimated 66% reduction in thromboembolic events relative to CHADS₂ predicted risk. This is a preliminary study of patients with contraindication/intolerance to anticoagulation. The authors note that the results should be confirmed in larger prospective registries and randomized trials in this patient population.

Huang et al. (2017) reported on a single center, prospective, observational study to evaluate the procedural feasibility, safety and 12-month outcomes of the WATCHMAN LAA Occlusion Device in 106 nonvalvular atrial fibrillation (NVAF) patients with high risk for stroke. There was follow-up at one, three, six and 12 months after discharge. A transesophageal echocardiograph was performed at 45 days after implantation. The procedural success rate was 94.3% (100/106), and the occlusion rate was 100.0% (100/100). There were one tamponade, one ischemic stroke, and eight minor pericardial effusions during hospitalization. In the 12-month follow-up period, two patients developed a thrombus layer on the device that resolved with additional anticoagulation: one with visible device-thrombus experienced transient ischemic stroke, and one had a hemorrhagic stroke with no deaths in the study. The overall survival rate was 100.0%, and non-major adverse event rate of 95.0% (95/100). In this study, the expected annual rate of ischemic stroke risk in these patients according to the CHA₂DS₂-VASc score was 4.0%, while the observed ischemic stroke rate was 2.0% per year. The authors note that large multi-center trials and long-term follow-up are needed to evaluate the safety and efficacy of this application.

Betts et al. (2017) reported on a retrospective study assessing the feasibility and long-term efficacy of left atrial appendage occlusion (LAAO) in 371 patients in eight centers in the United Kingdom. The device choice was Watchman in 63% of cases, Amplatzer Cardiac Plug in 34.7%, Lariat in 1.7%, and Coherex WaveCrest in 0.6%. The 343 patients who received an LAAO device were followed up for 24.7 ± 16.07 months. The overall procedure success was 92.5%, with major events in 3.5% of cases. A significant improvement in procedure success (from 89.2% to 95.7%; P = 0.018) and reduction of acute major complications (from 6.5% to 0.5%; P = 0.001) were observed between procedures in the first and the second half of the recruitment time. An annual 90.1% relative

risk reduction (RRR) for ischemic stroke, an 87.2% thromboembolic events RRR, and a 92.9% major bleeding RRR were observed, if compared with the predicted annual risks based on CHADS₂, CHA₂DS₂-Vasc, and HAS-BLED scores, respectively. The study was limited by retrospective nature and lack of randomization.

Chen et al. (2017) reported on a retrospective study was designed to compare the feasibility and safety of left atrial appendage closure (LAAC) in primary and secondary stroke preventions. The study included 122 non-valvular atrial fibrillation (AF) patients with CHA₂DS₂-VAsc ≥ 1 selected for percutaneous LAAC operations. Outcome observations of primary and secondary stroke preventions with Watchman devices were analyzed and compared with 68 for primary stroke prevention and 47 for secondary prevention (included in the secondary prevention group when they had previous histories of stroke/TIA or infarct foci identified by head CT/MRI scan). Trans-esophageal echocardiography (TEE) was performed at 45 days. Both the CHA₂DS₂-VAsc score and the HASBLED score were significantly higher in the secondary prevention group (4.09 ± 1.06 vs. 1.93 ± 1.09 for CHA₂DS₂-VAsc and 1.83 ± 1.03 vs. 1.26 ± 0.87 for HASBLED, $P < 0.01$). In both groups LAAC were achieved with high successful rate (98.53% in the primary prevention group and 100% in the secondary prevention group, $P > 0.05$) and low complication rates. In median follow-up of 12 months, stroke rates were found to be at low level in both groups (1.47% in primary prevention group vs. 2.13% in secondary prevention group, $P > 0.05$). Limitations of the study include the lack of comparator group, and that it is a retrospective study. The authors note that prospective clinical trials with larger sample size and longer follow-up period are needed to study the efficacy and safety of LAAC in secondary stroke preventions.

Sahay et al. (2017) reported on a network meta-analysis to assess the efficacy and safety of LAAC compared with other strategies for stroke prevention in patients with AF. The review included randomized controlled trials comparing warfarin with placebo, antiplatelet therapy (APT) or Non-vitamin K antagonist oral anticoagulants (NOAC) in patients with AF using meta-analysis guidelines. Two major trials of LAAC were also included and a network meta-analysis with indirect comparison was performed to compare the impact of LAAC on mortality, stroke/systemic embolism (SE) and major bleeding in relation to medical treatment. The network meta-analysis included 19 RCTs (87,831 patients) with AF receiving anticoagulants, APT, placebo or LAAC. Indirect comparison with network meta-analysis using warfarin as the common comparator revealed efficacy benefit that favored LAAC as compared with placebo (mortality: HR 0.38, 95% CI 0.22 to 0.67, $p < 0.001$; stroke/SE: HR 0.24, 95% CI 0.11 to 0.52, $p < 0.001$) and APT (mortality: HR 0.58, 95% CI 0.37 to 0.91, $p = 0.0018$; stroke/SE: HR 0.44, 95% CI 0.23 to 0.86, $p = 0.017$) and similar to NOAC (mortality: HR 0.76, 95% CI 0.50 to 1.16, $p = 0.211$; stroke/SE: HR 1.01, 95% CI 0.53 to 1.92, $p = 0.969$). LAAC showed comparable rates of major bleeding when compared with placebo (HR 2.33, 95% CI 0.67 to 8.09, $p = 0.183$), APT (HR 0.75, 95% CI 0.30 to 1.88, $p = 0.542$) and NOAC (HR 0.80, 95% CI 0.33 to 1.94, $p = 0.615$). The authors note that the findings of this meta-analysis suggest that LAAC is superior to placebo and APT, and comparable to NOAC for preventing mortality and stroke or SE, with similar bleeding risk in patients with nonvalvular AF. In addition, they note that these results should be interpreted with caution and more studies are needed to further substantiate this advantage, in view of the wide CIs with some variables in the current meta-analysis.

Saw et al. (2017) reported on a study to evaluate the safety and efficacy of WATCHMAN device for left atrial appendage (LAA) closure in 106 patients with nonvalvular atrial fibrillation (AF) and contraindications to anticoagulation. Indications for LAA closure were CHADS₂ ≥ 1 or CHA₂ DS₂ -VAsc ≥ 2 , and a contraindication/intolerance to or failure on anticoagulation. Follow-up imaging was performed one to six months post-procedure. The mean age of patients was 74.8 ± 7.7 , mean CHADS₂ score was 2.8 ± 1.2 , CHA₂ DS₂ -VAsc score was 4.3 ± 1.5 , and HASBLED score was 3.2 ± 1.2 . Indications for LAA closure were prior bleeding 89.6% (87 major bleeding and 8 minor bleeding), 9.4% were deemed high risk for bleeding, and 0.9% with recurrent strokes on warfarin. Procedural success was 97.2% (103 of 106), with one device embolization, one implant failure due to inadequate LAA depth, and one cardiac perforation requiring surgical repair before WATCHMAN implantation. The composite major safety event-rate was 1.9% (1 death and 1 device embolization). Antithrombotic therapy post-implant included dual antiplatelet therapy in 76 of 103 (73.8%). Mean follow-up was 210 ± 182 days; there were two transient ischemic attacks, with estimated 66% reduction in thromboembolic events relative to CHADS₂ predicted risk. The authors note that LAA closure with the WATCHMAN device for patients with nonvalvular AF and contraindications to OAC is safe and effective, and the results should be confirmed in larger prospective registries and randomized trials in this population.

Noelck et al. (2016) reported on a systematic review benefits and harms of surgical or percutaneous LAA exclusion procedures. The review included controlled clinical trials that assessed the effectiveness of percutaneous LAA exclusion procedures and to assess the harms of percutaneous LAA procedures cohort and registry studies with 50 or more patients were included. For percutaneous interventions, the review included two randomized controlled studies and 11 registry studies. The findings note that there is low-strength evidence that percutaneous LAA exclusion is associated with a similar risk of long-term stroke and mortality as continued oral anticoagulation therapy. The finding is based on trials of one device (Watchman) studied in patients without contraindications to oral anticoagulant therapy. Most patients who received the Watchman device were able to discontinue oral anticoagulant therapy after undergoing follow-up transesophageal echocardiography (TEE) showing persistent closure of the LAA at three to six months. The review found that there is moderate strength evidence that a substantial proportion of patients undergoing various percutaneous LAA exclusion procedures experienced serious periprocedural harms with insufficient evidence to determine whether factors such as operator experience, patient selection criteria, or choice of device can modify these risks. In addition, it was noted that there is insufficient data to assess the balance of benefits and harms of percutaneous LAA exclusion procedures in patients who are ineligible for long-term oral anticoagulation therapy.

Boersma et al. (2016) reported on peri-procedural outcomes of up to 30-days from the prospective, multicenter registry (EWOLUTION). Baseline/implant data were available for 1021 subjects with high risk of stroke and moderate-to-high risk of bleeding. The device was successfully deployed in 98.5% of patients with no flow or minimal residual flow achieved in 99.3% of the implanted patients. Thirty-one serious adverse events (SAEs) were noted in 28 subjects within 1 day of the procedure. The overall 30-day mortality rate was 0.7%. The most common SAE that occurred within 30 days of the procedure was major bleeding requiring transfusion. The incidence of SAEs within 30 days was lower for subjects deemed to be ineligible for oral anticoagulation therapy (OAT) compared with those eligible for OAT (6.5 vs. 10.2%, $P = 0.042$). The study is limited by lack of randomization, and short term follow-up. Boersma et al. (2017) reported on one-year follow-up of the EWOLUTION trial. At one year, mortality was 9.8%, noted by the author that is reflected the advanced age and comorbidities in the population. Device thrombus was observed in 28 patients at routine TEE (3.7%) and was not correlated with the drug regimen ($P=.14$). Ischemic stroke rate was 1.1% (relative risk 84% vs estimated historical data); the major bleeding rate was 2.6% and was predominantly (2.3%) nonprocedure/device related.

A noninferiority randomized, controlled trial (RCT) compared LAA closure with Watchman device to warfarin treatment in patients with non-valvular atrial fibrillation (NVAf), the PROTECT AF trial (Holmes, et al., 2009; Reddy, et al., 2013a; Reddy, et al. 2014). The trial included 707 patients, randomized 2:1, with the device group $n=463$ and warfarin group $n=244$ and a follow-up time was 3.8 ± 1.7 years (Reddy et al., 2014). Inclusion criteria: age ≥ 18 years; paroxysmal, persistent, or permanent NVAf and eligible for warfarin treatment; and, CHADS₂ score ≥ 1 . In the Watchman group the device implanted under transesophageal echocardiography (TEE) guidance with concomitant warfarin and Aspirin (ASA) (81-325 mg/day) for 45 days, on day 45, warfarin stopped, clopidogrel (75 mg/day) started until six month visit and then only ASA continued. In the warfarin group warfarin treatment was provided with a target INR 2-3. The primary efficacy outcome was stroke, systemic embolization, or cardiovascular death. The primary safety outcome was a composite of major bleeding events and procedure-related complications. At mean follow-up of 3.8 years, there were 39 events in 463 pts (8.4%) in the device group for primary event per 100 patient/years (pt/yrs), compared with 34 events in 244 patients (13.9%) for primary event rate of 3.8 in 100 pt/yrs in warfarin group. In the primary efficacy outcome, there was a noninferiority $>99\%$, and in the primary safety endpoint a noninferiority $>98\%$. Complications included in the Watchman group: serious pericardial effusion (4.8%); major bleeding (4.8%); procedure related ischemic stroke (1.3%); device embolization (0.6%); and hemorrhagic stroke (0.6%). In the warfarin group: major bleeding (7.4%); and, hemorrhagic stroke (3.7%). This study demonstrated the noninferiority of LAA closure compared to warfarin treatment. The study was limited in that it included warfarin, but did not include a comparison with the newer anticoagulants. The study included patients with warfarin, but does not address the patients who are unable to take anticoagulants.

A noninferiority RCT of that compared LAA closure with Watchman device and long-term warfarin treatment in pts with NVAf, the PREVAIL study (Holmes, et al., 2014). The study included 407 patients (randomized 2:1); with 68 patients enrolled through roll-in process with the Watchman group, $n=269$ and warfarin group, $n=138$. The follow-up time was a median of 12 months. The inclusion criteria included: NVAf; CHADS₂ ≥ 2 or 1 CHADS₂ plus 1 high-risk characteristic. In the Watchman group, the device was implanted guided by fluoroscopy and

TEE; post-implant patients were treated with warfarin and ASA for 45 days; TEE performed at 45 days, 6 months, and 12 months. Warfarin was discontinued if the day 45 TEE documented closure of LAA or residual peri-device flow <5 mm and no definite visible large thrombus on device; then clopidogrel 75 mg/day and ASA 81-325 mg/day was prescribed until six months when clopidogrel discontinued. In the warfarin group warfarin treatment was given with target INR 2.0-3.0. At 18 months, the rate of the first coprimary efficacy endpoint (composite of stroke, systemic embolism [SE], and cardiovascular/unexplained death) was 0.064 in the device group versus 0.063 in the control group and did not achieve the prespecified criteria noninferiority. The rate for the second coprimary efficacy endpoint (stroke or SE >7 days' post-randomization) was 0.0253 versus 0.0200 achieving noninferiority. Early safety events occurred in 2.2% of the Watchman arm. Complications (reported for Watchman-group only) (% of patients): device embolization (0.7%); arteriovenous fistula (0.4%); cardiac perforation (0.4%); pericardial effusion with cardiac tamponade (0.4%); major bleed requiring transfusion (0.4%). Noninferiority was not achieved for overall efficacy in this study. The patients in this study were required to be candidates for long-term anticoagulation to facilitate randomization against a control group treated with warfarin. The trial does not address the safety and efficacy of LAA occlusion when anticoagulation is contraindicated. In addition, the study does not include comparison with new oral anticoagulants.

Hayes published a technology assessment for the use of percutaneous LAA closure devices to reduce risk of stroke in patient with atrial fibrillation (AF) (Hayes 2015; 2016; 2017). It was noted that among the four studies that evaluated the efficacy of Watchman in stroke prevention in patients with non-valvular AF (NVAf), the 2 RCTs found this device to be noninferior compared with warfarin OAC in almost all primary measures. Both uncontrolled studies that compared observed versus expected stroke rates reported a lower observed rate in patients implanted with the Watchman device; however, neither study included a statistical test of significance. Regarding safety, LAA closure with the Watchman device is associated with a low but measurable risk of significant procedural/device-related complications such as major bleeding, pericardial effusion, stroke, device embolization, and cardiac perforation or tamponade. The conclusion included these findings regarding the Watchman device:

- Available evidence supports the use of the Watchman device for its FDA-approved indication in LAA closure.
- Since following implantation of the Watchman device patients must continue on warfarin therapy for approximately 45 days, there are very limited data on if and how to use the Watchman device in patients with absolute contraindications to warfarin.
- There would be a benefit from randomized studies that compare device-mediated LAA closure against treatment with the newer OACs and that test the use of the newer OACs as an adjunct to LAA closure.
- Trials are needed to help identify the patient subgroups that would most benefit from LAA closure.

Professional Societies/Organizations

American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS): These organizations published joint guidelines for the management of patients with atrial fibrillation (January, et al., 2014). The guidelines include a discussion of percutaneous occlusion of the LAA but do not provide specific recommendations regarding the use of these devices.

American Heart Association (AHA)/American Stroke Association (ASA): Joint guidelines from these organizations for the primary prevention of stroke include the following recommendations regarding LAA closure (Meschia, et al., 2014):

- closure of the LAA may be considered for high-risk patients with AF who are deemed unsuitable for anticoagulation
- performed at a center with low rates of periprocedural complications
- the patient can tolerate the risk of at least 45 days of post-procedural anticoagulation

(Class IIb; Level of Evidence B)

Level of evidence B: limited populations evaluated. Data derived from a single randomized trial or nonrandomized studies.

Class IIb: recommendation's usefulness/efficacy less well established; greater conflicting evidence from single randomized trial or nonrandomized studies

Use Outside of the US

Canadian Cardiovascular Society (CCS): The CCS published guidelines for the management of atrial fibrillation (Verma, et al., 2014). The guidelines note the following regarding LAA closure devices:

- LAA closure devices are not currently approved for use in Canada.
- It is suggested that these non-approved LAA closure devices not be used, except in research protocols or in systematically documented use protocols in patients at high risk of stroke (CHADS₂ score ≥ 2) for whom antithrombotic therapy is precluded (Conditional Recommendation, Low-Quality Evidence).

European Society of Cardiology (ESC): The ESC published updated guidelines for management of atrial fibrillation (Kirchhof, et al., 2016). The guidelines noted:

Recommendations for occlusion or exclusion of the left atrial appendage:

- After surgical occlusion or exclusion of the LAA, it is recommended to continue anticoagulation in at-risk patients with AF for stroke prevention.

Class I*

Level B

- LAA occlusion may be considered for stroke prevention in patients with AF and contra-indications for long-term anticoagulant treatment (e.g. those with a previous life-threatening bleed without a reversible cause).

Class IIb*

Level B

- Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery.

Class IIb*

Level B

- Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients undergoing thoracoscopic AF surgery.

Class IIb*

Level B

*Class of recommendations:

Class I - Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.

Class IIb - established by evidence/opinion. Usefulness/efficacy is less well established by evidence/opinion.

Level of evidence:

B Data derived from a single randomized clinical trial or large non-randomized studies.

European Heart Rhythm Association (EHRA)/European Association of Percutaneous Cardiovascular Interventions (EAPCI): EHRA/EAPCI published expert consensus statement on catheter-based left atrial appendage occlusion (Meier, et al., 2014). The statement includes the following:

- The main indication for LAA occlusion is AF with a CHADS₂ score ≥ 1 or CHA₂-DS₂-VASc score ≥ 2 and a relative or absolute contraindication to prolonged oral anticoagulation.
- Tolerance for at minimum several weeks of dual antiplatelet therapy, usually followed by lifelong single antiplatelet drug therapy.

National Institute for Health and Care Excellence (NICE): NICE clinical guidelines for the management of atrial fibrillation include the following recommendations regarding LAA closure (2010):

- Consider left atrial appendage occlusion (LAAO) if anticoagulation is contraindicated or not tolerated and discuss the benefits and risks of LAAO with the person.
- Do not offer LAAO as an alternative to anticoagulation unless anticoagulation is contraindicated or not tolerated.

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Chronic baroreceptor stimulation of the carotid sinus (CPT codes 0266T, 0267T, 0268T, 0269T, 0270T, 0271T, 0272T, 0273T)

The Barostim[®] neo implantable device (CVRx, Minneapolis, MN) is proposed to address cases of unmet treatment needs in patients with drug resistant hypertension. The Barostim neo device has replaced the Rheos Baroreflex Hypertension device. The device consists of an implantable pulse generator (IPG), one connecting lead wire, and an external wireless programmer system that allows physicians to modify device therapy. It is implanted under the skin beneath the collar bone with the lead positioned outside the carotid artery to conduct energy from the IPG to carotid baroreceptors. Activated baroreceptors signal the brain to respond to a rise in blood pressure. The brain responds by stimulating pathways of the autonomic nervous system responsible for arterial vessel dilation, heart rate, and fluid excretion. The device is also being investigated for use in heart failure.

U.S. Food and Drug Administration (FDA)

December 2014 the Barostim neo[®] Legacy System received humanitarian device exemption (HDE). The device is indicated for use in patients with resistant hypertension who have had bilateral implantation of the Rheos[®] Carotid Sinus Leads Models 1010R, 1010L, 1014L, and 1014R (which have been discontinued and are obsolete) and were determined responders in the Rheos[®] pivotal clinical study.

Literature Review

Wallbach et al. (2016) reported on a prospective study that evaluated ambulatory BP measurement (ABPM) data in patients with therapy-refractory hypertension (HTN) treated with the Baroreflex activation therapy (BAT) neo device. ABPM was performed before BAT implantation and six months after initiation of BAT. A total of 51 patients were included into this study, with seven dropping out from analysis. After six months, 24-hour ambulatory systolic (from 148 ± 17 mm Hg to 140 ± 23 mm Hg, P<0.01), diastolic (from 82 ± 13 mm Hg to 77 ± 15 mm Hg, P<0.01), day- and night-time systolic and diastolic BP (all P ≤ 0.01) decreased while the number of prescribed antihypertensive classes could be reduced from 6.5 ± 1.5 to 6.0 ± 1.8 (P=0.03). Heart rate and pulse pressure remained unchanged. BAT was equally effective in reducing ambulatory BP in all subgroups of patients. The authors note that randomized controlled trials are needed to evaluate BAT effects on ABPM in patients with resistant hypertension accurately. This study is limited by the small number of subjects and lack of randomization.

Biognano et al. (2011) published the pivotal study regarding Baroreflex activation therapy (BAT) of the Rheos device. Patients were randomized to receive either active BAT (group A, n=181) or deferred BAT (group B, n=84) with the Rheos system. Active BAT was initiated one month after implantation, while deferred BAT was started seven months after implantation. This design allowed short term comparison between BAT and medical management. The coprimary endpoints: 1) acute systolic blood pressure (SBP) responder rate at 6 months; 2) sustained responder rate at 12 months; 3) procedure safety; 4) BAT safety; and 5) device safety. At 6-month follow-up, 54% of active group patients and 45% of those not receiving active therapy achieved the preset acute efficacy goal of at least 10 mm Hg reduction in (SBP); between-group comparison was not statistically significant. The 30-day rate of procedure- or device-related serious adverse events was 25.5%, which did not meet the preset objective performance criterion (OPC) for procedural safety. Although the 12-month sustained efficacy endpoint was met, this endpoint was assessed by comparing Group A patient outcomes with OPC rather than with Group B outcomes, leading to difficulty in interpretation of the clinical relevance of this result. The long-term device safety and short-term BAT safety primary outcomes were met.

Following completion of the randomized Rheos Pivotal Trial, Bakris et al. (2012) conducted an open-label, nonrandomized single-arm follow-up to assess safety and efficacy of BAT. Blood pressure reductions were measured relative to a pre-implant baseline as well as the results achieved at the completion of 1 year of follow-up in the randomized phase. Clinically significant responder status was assessed according to FDA-mandated criteria. Of the 322 patients implanted, 76% (n=245) qualified as clinically significant responders, an additional 10% were indeterminate. Among long-term responders receiving BAT, the mean blood pressure drop was 35/16 mm Hg. Among responders, 55% achieved goal blood pressures (<140 mm Hg or <130 mm Hg in diabetes or kidney disease). Blood pressures of all active patients remained stable from completion of the randomized phase through long-term follow-up. BAT substantially reduced arterial pressure for most patients participating in the Rheos Pivotal Trial. This blood pressure reduction or goal achievement was maintained over long-term follow-up of 22 to 53 months.

Use Outside of the US

No relevant information

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Endovascular Repair of Visceral Aorta for Abdominal Aortic Aneurysm (including planning) (CPT Codes 34806, 34839, 34841, 34842, 34843, 34844, 34845, 34846, 34847, 34848, 93982) (Codes 34806, 93982 deleted 12/31/2017)

The conventional treatment for AAA has been open surgical repair. Open surgical repair involves transabdominal surgery, exposure of the aneurysm, cross-clamping the aorta, resection of the aneurysm, and placement of graft prosthesis. Endovascular AAA repair developed as a minimally invasive alternative to open surgical repair in patients with suitable anatomy. Endovascular repair of infrarenal abdominal or aortoiliac AAA has demonstrated reduced rates of perioperative mortality and morbidity compared to open surgical repair, with equivalent long-term aneurysm-related mortality, although this approach is associated with higher rates of reintervention, and requires long-term radiological monitoring. Endovascular repair may be a reasonable option for selected patients with suitable anatomy for whom the risk/benefit ratio favors endovascular repair.

The use of fenestrated grafts (e.g., Zenith® Fenestrated AAA Endovascular Graft) has been investigated for the treatment of patients with AAA involving the visceral arteries. These grafts include fenestrations, or scallops, in the graft material that allow the proximal edge of the material to be placed above the renal arteries while permitting blood flow to vessels accommodated by the fenestrations. Evidence published in the medical literature consists primarily of registry data, small feasibility studies, and case series with limited outcome data. Additional evidence is needed to determine the safety, efficacy, and long-term outcomes of this procedure and to determine how this approach compares to surgical repair.

U.S. Food and Drug Administration (FDA)

A number of devices have received approval through the FDA Premarket Approval (PMA) process for endovascular treatment of AAA, including the following:

- AneuRx® Stent Graft System (Medtronic Vascular, Santa Rosa, CA)
- Zenith® AAA Endovascular Graft and H&L-B One-Shot™ Introduction System (Cook Incorporated, Bloomington, IN)
- EXCLUDER™ Bifurcated Endoprosthesis (W.L. Gore & Associates, Inc., Flagstaff, AZ)
- Endologix PowerLink® System (Endologix, Inc., Irvine, CA)
- Talent™ Abdominal Stent Graft System (Medtronic Vascular, Santa Rosa, CA)
- Endurant Stent Graft System (Medtronic Vascular, Santa Rosa, CA)

The Zenith® Fenestrated AAA Endovascular Graft (with the adjunctive Zenith Alignment Stent) received FDA PMA approval on December 22, 2011. The Zenith graft is indicated for the endovascular treatment of patients with abdominal aortic or aortoiliac aneurysm having morphology suitable for endovascular repair, including:

- Adequate iliac/femoral access compatible with required introduction systems
- Nonaneurysmal infrarenal aortic segment (neck) proximal to the aneurysms with:
 - Length ≥ 4 mm and unsuitable for a non-fenestrated graft
 - Diameter ≤ 31 mm and ≥ 19 mm
 - Angle < 45 degrees relative to long axis of aneurysm
 - Angle < 45 degrees relative to axis of suprarenal aorta
- Ipsilateral iliac artery fixation site > 30 mm in length and between 9- 21 mm in diameter
- Contralateral iliac artery distal fixation site >30 mm in length and between 7 – 21 mm in diameter

The Zenith Alignment Stent is indicated for use as an adjunct to the Zenith Fenestrated AAA Endovascular Graft to secure positive alignment of fenestrations or scallops with the orifice of aortic branch vessels having diameters ranging from 3 to 8 mm. Unlike the standard Zenith AAA Endovascular Graft, the Zenith Fenestrated AAA graft has fenestrations or scallops in the graft material, which allow the proximal edge of graft material to be placed above the renal arteries while still permitting blood flow to vessels accommodated by the fenestrations or scallops. In order to account for anatomical variation, each proximal body graft is made to order for a specific patient. The Zenith fenestrated graft has been available outside the U.S. since 2002.

The CardioMEMS EndoSure™ Wireless AAA Pressure Measurement System was approved for marketing through the 510(k) process on October 12, 2006 for the measurement of intrasac pressure during endovascular

AAA repair and for use as an adjunctive tool in the detection of intraoperative leaks. In a subsequent approval on March 15, 2007, measurement of intrasac pressure during thoracic aortic aneurysm repair was added as an intended use.

According to the 510(k) summary, the sensor is implanted in the aneurysm sac during stent graft deployment and is left in place in the excluded portion of the aneurysm as a permanent implant. The main body of the sensor is composed of fused silica coated in silicone. Nitinol loops extend from and surround the sensor body. The sensor is interrogated using the antenna of the EndoSure Electronics System. Once the signal is acquired, a pressure waveform and numerical pressure data are displayed on the touch-screen, and a printout of the data and waveform is generated.

Literature Review

Hayes published a technology directory report on endovascular repair of abdominal aortic aneurysms (AAA) (Hayes 2013; 2016; 2017). The review included 11 randomized controlled trials (RCTs). The RCTs of endovascular aneurysm repair (EVAR) indicate that outcomes are comparable with open surgery for large aneurysms in need of repair, with surveillance for small aneurysms, and with open surgery for the treatment of ruptured aneurysms. The six trials that compared EVAR with open surgery for unruptured AAAs generally found lower 30-day mortality rates with EVAR than with open surgery, but intermediate-term (one to four years) survival and long-term survival (5+ years) were not different between groups, which suggests that the benefit of EVAR occurs in the immediate postoperative period. Of the five studies that reported health-related quality of life (HRQL) results, three found an early benefit with EVAR that was not maintained past three to six months. Complication rates were not consistently different between groups, with the exception that reintervention rates were higher with EVAR than with open surgery in several trials. In the two RCTs that compared EVAR with surveillance for small unruptured AAAs, no differences were observed between groups in 30-day mortality or intermediate-term survival. One study found significantly higher HRQL scores in the EVAR group than in the surveillance group at six months, but the differences were nonsignificant as the study progressed with both studies stopped early based on futility analyses. In the single study that compared EVAR with no treatment for large unruptured AAAs in patients unfit for open surgery, 7% of patients died within 30 days due to EVAR procedure-related causes. No differences between groups were noted in survival or HRQL after up to four years of follow-up (median, 2.4 years), but complications were significantly higher in the EVAR group than in the surveillance group. Two small RCTs (32 and 116 patients) compared EVAR with open repair of ruptured AAA, but neither study found differences in 30-day mortality rates between groups or in overall rates of moderate or severe complications. Mortality rates also did not differ in the study that followed patients for up to two years. The review noted limitations of the RCTs that included the lack of blinding procedures for patients and assessors for many outcome measures. In addition, the studies included a preponderance of males; although no systematic differences in outcomes between men and women were apparent. The surgeries in these studies were performed by experienced surgical teams, and it is uncertain whether these results would generalize to groups with less experienced surgeons. Additionally, in the studies that included surveillance groups for small AAAs, screening procedures were required every six months to monitor AAA size and growth rate; it is therefore uncertain whether the results with the surveillance group would apply to patients with AAAs that are screened less frequently.

Endovascular Repair Using a Fenestrated Graft: The British Society for the Endovascular Therapy and the Global Collaborators on Advanced Stent-Graft Repair (GLOBALSTAR) Registry published early results of endovascular repair of juxtarenal aortic aneurysms using the Zenith fenestrated graft in the United Kingdom (2012). Data from 318 patients treated at 14 experienced centers (i.e., > 10 procedures) were retrospectively studied. The primary procedural success rate was 99% (316/318); perioperative mortality was 4.1%; and intraoperative target vessel loss was observed in 5 of 889 target vessels (0.6%). The early reintervention rate (i.e., <30 days) was 7%. There were 11 deaths during the follow-up, but none were aneurysm-related. Freedom from target-vessel loss at one, two, and three years was 93%, 91%, and 85%, respectively, and freedom from late secondary intervention (> 30 days) was 90%, 86%, and 70% at one, two and three years, respectively. The authors stated that these results support continued use and evaluation of this technique for juxtarenal aneurysms, but illustrate the need for a more robust evidence base.

Amiot et al. (2010) conducted a retrospective analysis to evaluate the medium-term outcomes of aortic aneurysm repair using the Zenith fenestrated graft in 16 French academic centers (n=134). Patients were considered to be

at high risk for open surgical repair. The median aneurysm size was 56 mm (range 45-91 mm), and the median patient age was 73 years (range 43-91 years). A total of 403 visceral vessels were treated, including 265 renal arteries. One early conversion to surgery was required. Angiography immediately following the procedure demonstrated patency in 398 of 403 target vessels. The 30-day mortality was 2%. Imaging prior to discharge revealed 16 (12%) endoleaks (3 type I, 12 type II, and 1 type III). Transient or permanent dialysis was required in 4 (3%) and two (1%) patients, respectively. During a median follow-up of 15 months (range 2-53 months), no aneurysms ruptured or required open conversion. Aneurysm sac size decreased by more than 5 mm in 52%, 65.6%, and 75% of patients at one, two and three years, respectively. Three patients had sac enlargement within the first year associated with persistent endoleaks. Four renal artery occlusions were detected during follow-up, and 12 procedures related to reintervention were performed in 12 patients, including six to correct endoleaks and five to correct threatened visceral vessels. Twelve of 131 patients died during follow-up; none of these were aneurysm related.

Greenberg et al. (2009) reported intermediate results of a multicenter prospective case series to assess the safety and efficacy of the Zenith fenestrated devices (n=30) in patients with juxtarenal AAA. Inclusion criteria consisted of aortic or aortoiliac aneurysms with diameter greater than five cm, or with aortic or aortoiliac aneurysms with a history of growth greater than 0.5 cm per year or clinical indication for AAA repair. Customized devices were designed for each patient based on calculations derived from computed tomography (CT) scan data. A total of 77 visceral vessels were accommodated by fenestrations within the sealing segment of the grafts. The most common design accommodated two renal arteries and the superior mesenteric artery (66.7%). Prostheses were successfully implanted in all patients. Of the 30 patients, 27 were available for follow up at 12 months, and 23 were available at 24 months. There were no aneurysm related deaths, aneurysm ruptures, or conversions during the follow-up period. There were no type I or type III endoleaks reported. Type II endoleaks were reported in six patients (26.1%) at 12 months, and in four (20.0%) at 24 months. None of the patients had aneurysm growth > 5 mm. Aneurysm size at 24 months decreased in 16 of 23 patients (69.6%) and was stable in the remaining patients. A renal event occurred in eight patients. Secondary interventions were performed in five patients. No patients experienced renal failure requiring dialysis. The authors concluded that the intermediate term results of this multicenter study are concordant with previous single-center studies and support the concept the placement of fenestrated endovascular grafts is safe and effective at centers with experience in endovascular repair and renal/mesenteric stent placement.

An Agency for Healthcare Research and Quality (AHRQ) evidence report/technology assessment (Wilt et al., 2006) compared endovascular and open surgical repairs for AAA. Randomized controlled trials of open surgical repair, endovascular repair, or active surveillance; systematic reviews; nonrandomized U.S. trials; and national registries were used to assess clinical outcomes. The assessment concluded that for AAA < 5.5 cm in diameter, active surveillance with delayed open surgical repair results in equivalent mortality, but less morbidity, due to fewer interventions, compared to immediate open surgical repair. Endovascular repair of aneurysms ≥ 5.5 cm has not been shown to improve long-term survival or health status compared to open surgical repair, although perioperative outcomes are improved. The assessment also stated that endovascular repair does not improve survival in patients who are medically unfit for open surgical repair. Endovascular repair is associated with more complications, need for reintervention, and monitoring compared to open surgical repair or no intervention. The AHRQ report recommended U.S. randomized controlled trials be conducted with approved endovascular repair devices to evaluate patient outcomes.

CardioMEMS EndoSure Wireless AAA Pressure Measurement System: Published evidence on the use of the CardioMEMS system consists of several diagnostic cohort studies with short-term preliminary results (Hoppe et al., 2008, n=12; Silveira et al., 2008, n=25; Ohki et al., 2007, n=76). The safety and clinical utility of this technology in the intraoperative or long-term monitoring of patients following endovascular aortic aneurysm repair has not been established.

Use Outside of the US
No relevant information.

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Endovascular repair of iliac artery bifurcation (CPT 0254T, 0255T) (Code 0255T deleted 12/31/2017, use 0254T to report):

Involvement of the common iliac arteries occurs in approximately 20% of patients with abdominal aortic aneurysms (AAA) and may present a challenge to endovascular treatment since it may compromise sealing and distal fixation of endoprostheses. Several techniques have been developed to achieve the goal of sealing the aneurysmal sac, with one of the techniques is developed of an endoprosthesis for use in the iliac arteries. A device that has been developed exclusively for use in the iliac arteries is the GORE® EXCLUDER® Iliac Branch Endoprosthesis (IBE) (W. L. Gore & Associates, Inc., Flagstaff, AZ). It is intended to be used in conjunction with the Gore Excluder abdominal aortic aneurysm (AAA) endoprosthesis to isolate the common iliac artery from the systemic blood flow and is intended to preserve blood flow to the external and internal iliac arteries and preserve pelvic perfusion (Hayes, 2017).

U.S. Food and Drug Administration (FDA)

The GORE® EXCLUDER® Iliac Branch Endoprosthesis (IBE Device) received FDA premarket (PMA) approval February 2016. It is indicated for use with the GORE® EXCLUDER® AAA Endoprosthesis to isolate the common iliac artery from systemic blood flow and preserve blood flow in the external iliac and internal iliac arteries in patients with a common iliac or aortoiliac aneurysm, who have appropriate anatomy that includes:

- Adequate iliac/femoral access
- Minimum common iliac diameter of 17 mm at the proximal implantation zone of the IBE
- External iliac artery treatment diameter range of 6.5-25 mm and seal zone length of at least 10 mm
- Internal iliac artery treatment diameter range of 6.5-13.5 mm and seal zone length of at least 10 mm
- Adequate length from the lowest major renal artery to the internal iliac artery to accommodate the total endoprosthesis length, calculated by adding the minimum lengths of required components, taking into account appropriate overlaps between components

Contraindications to the device include:

- Patients with known sensitivities or allergies to the device materials. All components of the GORE EXCLUDER Iliac Branch Endoprosthesis and the GORE EXCLUDER AAA Endoprosthesis contain ePTFE, FEP, nitinol (nickel-titanium alloy), and gold.
- Patients with a systemic infection who may be at increased risk of endovascular graft infection.

Literature review

van Sterkenburg et al. (2016) reported on a retrospective cohort analysis that analyzed procedural success and early outcome of endovascular treatment of a multicenter cohort of patients (n=46) with common iliac artery (CIA) aneurysms treated with the GORE EXCLUDER. The median diameter of the treated aneurysm was 40.5 (range, 25.0-90.0) mm and the mean procedural time was 198 ± 56 minutes. One implantation was not successful; two type 1b endoleaks were noticed, which resulted in procedural success rate of 93.5%. The two type 1b endoleaks spontaneously disappeared at 30 days and there was no 30-day mortality. Ipsilateral buttock claudication was present in two cases at 30 days and disappeared during follow-up. The incidence of reported erectile dysfunction was low and there was an absence of severe ischemic complications. After a mean follow-up of six months, data on 17 treated aneurysms were available: these showed two with a stable diameter, and 15 showed a mean decrease of 3.9 ± 2.2 mm (P<.001). Re-interventions were done in two patients (7.1%). The six-month primary patency of the internal component of the IBE device was 94%. The authors noted that prospective data with longer follow-up are awaited to establish the role of the device in the treatment algorithm of CIA aneurysms. Limitations of the study include small sample size and retrospective nature of the study.

Use Outside of the US

CE Marking for this product was issued in 2013.

European Society for Vascular Surgery: this organization published clinical guidelines for the management of abdominal aortic aneurysms (Moll, et al., 2011). Recommendations regarding the management of iliac aneurysms include:

- Coexisting iliac aneurysms should be treated concurrently with AAA. Isolated iliac aneurysms may be treated by either open or, preferentially, endovascular techniques. Intervention should be considered when the iliac diameter exceeds 3 cm. Iliac aneurysms should be repaired once the diameter exceeds 3 cm.

Level 3a, Recommendation C

- Endovascular treatment options should be considered in all patients and in defined subgroups this will include the consideration for iliac branch graft placement.

Level 3a, Recommendation C

Level 3A: systematic review (with homogeneity) of case-control studies

Recommendation C: Level 4 studies or extrapolations from level 2 or 3 studies (Extrapolations are where data are used in a situation that has potentially clinically important differences than the original study situation).

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Implanted Wireless Pulmonary Artery Sensor (e.g., CardioMEMS HF System) (HCPCS Codes C2624, C9741)

Implantable intracardiac pressure monitors are intended to complement conventional drug therapy for heart failure (HF) through intermittent monitoring, allowing more timely adjustments to medications, if needed. The CardioMEMS™ HF System (St. Jude Medical, Inc., St. Paul, MN, USA, formerly Champion HF Monitoring System as well as Heart Sensor; CardioMEMS, Inc., Atlanta, GA) is a 2 x 3.4 x 15mm sized device that allows monitoring of pulmonary artery (PA) pressure using a wireless sensor. The sensor has two wire loops extending from either side. It is inserted into the PA through a traditional right heart catheterization procedure. Once deployed, PA pressure measurements can be taken repeatedly and transmitted wirelessly without requiring right heart catheterization or other invasive procedures. The sensor requires no batteries and is intended to be a permanent implant.

To record measurements at home, the patient lies on top of a pillow with sensory equipment embedded. A recording device with a cable-connected remote control is placed within four to five feet of the pillow. The patient reclines on the pillow and is guided to an optimal position by the recording device. When positioning is adequate, the machine prompts the patient to start recording by pushing the remote control. According to the manufacturer, the patient must remain still while pressures are recorded for 18 seconds, during which the machine plays music, intended to relax the patient. When the reading is complete, the machine automatically transmits the information to the CardioMEMS website (St. Jude Medical, 2014).

U.S. Food and Drug Administration (FDA)

Although a number of implantable wireless sensors are in development the CardioMEMS™ HF system is the only device in this group that has received FDA approval. On May 28, 2014 the Food and Drug Administration (FDA) granted CardioMEMS, Inc.'s (formerly Atlanta, GA, now St. Jude Medical, Inc., St. Paul, MN) premarket approval (PMA P100045) for the CardioMEMS HF System which includes the CM2000 implantable PA Sensor/Monitor and transvenous catheter delivery system, the CM1000 Patient Electronics System (GSM), the CM1010 Patient Electronics System (GSM), and CM3000 Hospital Electronics System. According to the PMA, the device is indicated for wirelessly measuring and monitoring pulmonary artery (PA) pressure and heart rate in patients with New York Heart Association (NYHA) Class III HF who have been hospitalized for HF in the previous year. The FDA approval requires that the manufacturer conduct an additional prospective, multi-center, open-label trial conducted in the United States to examine the safety and effectiveness of CardioMEMS HF System in 663 adults with NYHA Class III Heart Failure (HF) who have experienced a heart failure hospitalization within the

past 12 months; of which a total of 420 will be women. Follow-up will be two years post implant with specified safety and effectiveness endpoints. Additionally a prospective, multi-center, open-label substudy conducted in the United States to examine safety and compare the postmarket effectiveness of CardioMEMS HF System to premarket is required by the FDA.

Literature Review

Data is limited in the published peer-reviewed scientific literature regarding the safety and effectiveness of the CardioMEMS HF System.

Hayes published a technology brief for wireless pulmonary artery pressure monitoring with CardioMEMS (CM) HF System for management of chronic heart failure (Hayes, 2016). The review included three clinical studies (n=12 to 550) that evaluated the accuracy, clinical utility, and safety of the CardioMEMS (CM) HF system for the management of patients with chronic heart failure. The system is a wireless implantable hemodynamic monitor (IHM) that measures pulmonary artery pressure (PAP) and heart rate in patients with heart failure (CM-IHM). Limitations of two poor-quality cohort studies included small numbers of patients, lack of data to calculate sensitivity, specificity, and predictive values, and use of echocardiography as a reference standard for diastolic PAP measurements. Although of good quality, the one randomized controlled trial was limited by a lack of data on any drug treatment modifications related to changes in patient management, and a lack of data on adverse events related to drug changes. It was found that overall, a low-quality body of evidence provides limited data suggesting that the CM-IHM system for patients with NYHA class III heart failure accurately monitors PAP, reduces heart failure-related hospitalizations through improved medical management over the first six months following implantation, and carries a minimal risk for serious adverse events.

Abraham et al. (2011) reported results of a randomized controlled trial (RCT): the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial. The outcomes of this trial were reviewed by the FDA for premarket approval of this device. Eligible patients underwent implantation of a wireless pulmonary artery (PA) sensor monitoring system (i.e., CardioMEMS). Five hundred fifty individuals were implanted and randomized to the treatment group (n=270, standard of care HF treatment, plus PA pressure readings) or to the control group (n=280, standard of care HF treatment). Daily PA pressure readings were taken at home by patients in each group and sent to a secure website. In the treatment group clinicians had access to these readings; in the control group clinicians were unable to access pressure readings. Assessment at one, three and six months, and every six-months thereafter included a physical examination, assessment of New York Heart Association class and quality-of-life assessment by use of the 21-question Minnesota Living with Heart Failure questionnaire and review of drugs.

The primary efficacy endpoint was the rate of heart failure-related hospitalizations during the six months after insertion of the pressure sensor in the treatment group versus the control group. The two primary safety endpoints were device-related or system-related complications. The mean follow-up was 15 months. At six months 83 heart-failure-related hospitalizations were reported in the treatment group compared with 120 in the control group ($p<0.0001$). During the entire follow-up (mean 15 months) the treatment group had a 39% reduction in heart-failure-related hospitalization compared with the control group ($p<0.0001$). Eight patients had device- or system-related complications (DSRC). Overall freedom from DSRC was 98.6%. Overall freedom from pressure-sensor failures was 100%. Survival rates in the treatment and control groups at six months were similar ($p=0.45$). Fifteen serious adverse events (AE) were reported, including, infection, bleeding, thrombosis, cardiac arrhythmias, one patient with cardiogenic shock, one atypical chest pain, and one delivery-system failure that required a snare to remove the delivery system. Data in this single clinical trial suggest improved shortterm outcomes; however, additional large blinded RCTs replicating these findings are required before use of a wireless pulmonary artery sensor monitoring system (e.g., CardioMEMS HF system) is incorporated into routine clinical practice.

Use Outside of the US

National Institute of Health Care and Excellence (NICE): NICE (2013) guidance on insertion and use of implantable pulmonary artery pressure monitors in chronic heart failure notes that current evidence on the safety and efficacy of the insertion and use of implantable pulmonary artery pressure monitors in chronic heart failure is limited in both quality and quantity. They recommend that this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

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Intravascular Catheter-Based Coronary Vessel or Graft Spectroscopy (CPT Code 0205T)

The leading cause of major morbidity and mortality is atherosclerotic cardiovascular disease, most commonly caused by thrombotic occlusion of a high-risk coronary plaque resulting in myocardial infarction or cardiac death, or embolization from a high-risk carotid plaque resulting in stroke (Alsheikh-Ali, 2010).

Near-infrared spectroscopy is proposed as a method to detect lipid and cholesterol deposits in coronary vessel walls. Ex vivo studies have demonstrated the feasibility of atherosclerotic lipid-rich plaque detection using near-infrared spectroscopy (NIRS). While near-infrared spectroscopy can collect data with rapid acquisition times, avoiding the need to obstruct blood flow it does not create an image of the vessel wall, which is a limitation of the device. Fibroatheromas that are thick capped or too small to be defined as lipid core plaques are major sources of false-positive readings (Alsheikh-Ali, 2010).

U.S. Food and Drug Administration (FDA)

The LipiScan Coronary Imaging System (InfraReDx, Inc., Burlington, MA) received FDA 510(k) approval in April 2008. The device is indicated for the near-infrared examination of coronary arteries.

Literature Review

Randomized controlled clinical trial data are lacking in the published peer-reviewed scientific literature. Waxman et al. (2009) reported initial results of the first-in-human uncontrolled validation study involving a catheter-based near-infrared spectroscopy system for the detection of lipid core coronary plaques (SPECTACL [SPECTroscopic Assessment of Coronary Lipid] trial). A total of 106 patients were enrolled in the study, spectroscopic data was obtained in 89 patients. Spectral similarity was demonstrated in 83% of available patients. The algorithm developed ex vivo identified the high-risk plaques in 60% of imaged segments in patients undergoing percutaneous coronary intervention. The authors note the feasibility of invasive detection of coronary lipid core plaques with this system.

Professional Societies/Organizations

Guidelines from the American Heart Association and the American College of Cardiology do not include guidance regarding use of intravascular catheter-based coronary vessel or graft spectroscopy to identify lipid core plaques or for any indication.

Use Outside of the US

No relevant information.

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Acoustic Cardiography (CPT code 93799)

Acoustic cardiography, also referred to as correlated audioelectric cardiography is a noninvasive diagnostic tool designed to be used in the evaluation of cardiac conditions such as left ventricular hypertrophy (LVH), acute and age-undetermined myocardial infarction (MI), cardiac arrhythmias, and detection of S3 and S4 heart sounds. An S3 heart sound may be associated with heart failure in patients over age 40. Acoustic cardiography is intended to augment physician auscultation, since S3 and S4 heart sounds may be difficult to hear in some patients. The device acquires, displays, and analyzes 12-lead electrocardiogram (ECG) and heart sound data (Collins et al., 2006; Kobza et al., 2008; Wagner et al., 2002; Warner et al., 2002).

Traditional diagnostic methods include physical examination and auscultation, 12-lead ECG laboratory examinations, measurement of biomarkers of cardiac damage, and imaging.

U.S. Food and Drug Administration (FDA)

The Eli 200+ Audicor (Mortara Instrument, Inc., Milwaukee, WI) is an interpretive electrocardiograph device designed to acquire, record and store cardiac data. The device uses Audicor Correlated Audioelectric Cardiography (COR) technology (Inovise Medical, Inc., Newberg, OR) to simultaneously acquire both 12-lead electrocardiogram (ECG) and heart sound data. The Eli 200+ Audicor received U.S. Food and Drug Administration (FDA) clearance to market as a Class II device through the 510(k) process on July 25, 2003. The device was considered a technology evolution and substantially equivalent to the ELI 200, Inovise's Cardiovisc Interpretive Software, and Hewlett Packard's 1514A ECG/Phono System.

The FDA 510(k) notification of clearance to market the Eli 200+ Audicor included the following indications for use:

- The device is indicated for use to acquire, analyze, display and print ECG and heart sound data (COR).
- The device is indicated for use to provide interpretation of the data for consideration by physicians.
- The device is indicated for use in a clinical setting by a physician or by trained personnel and is not intended as a sole means of diagnosis.
- The interpretations of ECG and heart sound data (COR) offered by the device are only significant when used in conjunction with physician over-read as well as consideration of all other relevant patient data.
- The device is intended for use on adult populations, typically symptomatic.
- The device is not intended to be used as a vital signs physiological monitor.

- The device is indicated for evaluation of cardiac conditions such as left ventricular hypertrophy (LVH), acute and age-undetermined myocardial infarction (MI), and detection of S3 and S4 heart sounds.

On October 31, 2003, the Audicor Upgrade System received FDA clearance as a Class II device through the 510(k) process. The Audicor Upgrade System is an add-on device used with Audicor Sensors in the V3 and V4 positions on the chest wall. The system consists of a pocket personal computer (PC) with proprietary software and can be used with several models of existing electrocardiographs to allow physicians access to the COR report, including graphical display of MI and LVH conditions, display of heart sound waveforms, and identification of S3 and S4 heart sounds.

The Zargis Acoustic Cardioscan (Zargis Medical Corporation, Princeton, NJ) received FDA approval through the 510(k) process on May 26, 2004. The system is an electronic auscultatory device intended to acquire, record, and analyze heart sounds. The system consists of an electronic stethoscope, notebook computer, software, printer and an isolation transformer. According to the FDA indications for use, the device acquires and records the acoustic signals of the heart and analyses these signals. The analysis procedure will identify specific heart sounds that may be present, including S1, S2, and suspected murmurs. The approval lists the Audicor system as a predicate device.

Literature Review

Published studies have evaluated the use of Cardiovisc diagnostic software, a predicate device and component of the Audicor System, for the detection of acute and prior MI (Wagner, et al., 2002; Andresen, et al., 2002). Published studies involving the Audicor system or correlated audioelectric cardiography are limited.

Wang reported on results of a prospective cohort study of 474 patients with heart failure (HF) to evaluate whether acoustic cardiography can identify HF patients at high risk for mortality. Acoustic cardiographic parameters included S3 score and systolic dysfunction index (SDI) (correlated closely with left ventricular systolic dysfunction). The event-free survival curves were plotted by Kaplan-Meier method and Cox regression analysis was used to identify independent predictors for all-cause mortality. With a mean follow-up of 484 days, 169 (35.7%) patients died and 126 (26.6%) were due to cardiac causes. After controlling for age, systolic blood pressure, hemoglobin, blood urea nitrogen, albumin, as well as ACEI and beta-blocker treatment in multivariate Cox regression analysis, SDI ≥ 5 and S3 score ≥ 4 were both independent predictors for all-cause mortality. Kaplan-Meier analysis showed that HF patients with SDI ≥ 5 or S3 score ≥ 4 had a significantly lower survival (52.2% vs. 69.2%, Log-rank $\chi^2(2)=18.07$, $P<0.001$; 56.8% vs. 68.6%, Log-rank $\chi^2(2)=10.58$, $P=0.001$, respectively) than those with lower SDI or S3 score. The study was limited by the lack of randomization. Limitations noted in the study included that adverse nonfatal outcomes including rehospitalization or severe medical complications were not evaluated in this study and further investigations focusing on prediction of subsequent cardiovascular events are warranted; BNP was not routinely measured in heart failure patients and not included as biomarker in the analysis; and, heart failure patients with atrial fibrillation were not excluded from our study.

Wang et al. (2013) reported the results of a prospective cohort study ($n=272$) to determine the diagnostic utility of acoustic cardiography in patients with heart failure (HF). Cohort subjects had hypertension ($n=94$), heart failure (HF) and normal ejection fraction (HRNEF, $n=109$, $EF\geq 50\%$) and HR and reduced EF (HRREF, $n=89$, $EF<50\%$). All participants received acoustic cardiography and echocardiography examinations. Acoustic cardiographic parameters included S3 score, electromechanical activation time (EMAT) and systolic dysfunction index (SDI). EMAT significantly differentiated HFNEF from hypertension (area under curve [AUC], 0.83; 95% confidence interval [CI], 0.77–0.89) with a sensitivity and specificity of 55% and 90%, respectively. An echocardiogram yield a sensitivity of 55% and 90% specificity. An SDI > 5.43 yielded 53% sensitivity and 91% specificity. The authors note that this technology may be helpful in identifying HF and its phenotypes when echocardiography is not available. The study is limited by small size, uncontrolled design and low sensitivity and specificity results.

Collins et al. (2009) conducted a multisite study to evaluate the effect of an S3 captured by acoustic cardiography on diagnostic accuracy and confidence in the diagnosis of acute decompensated heart failure in patients presenting to the emergency department (ED) with dyspnea ($n=995$). The study also evaluated the impact on patient prognosis. ED physicians who were initially blinded to all laboratory and acoustic cardiography results estimated the probability of acute decompensated heart failure on a scale of 0% to 100% on a visual analog scale. The visual analog scale was repeated after acoustic cardiography results were provided. Patients

were followed for 90 days to determine the relationship of the S3 to adverse events. The initial sensitivity, specificity, and accuracy for acute decompensated heart failure as a possible diagnosis were 89.0%, 58.2%, and 71.0%, respectively. Sensitivity, specificity, and accuracy for acoustic cardiography were 40.2%, 88.5%, and 68%, respectively. The authors concluded that acoustic cardiography S3 was specific to acute decompensated heart failure, but did not improve diagnostic accuracy, primarily because of the low sensitivity. In addition, the acoustic cardiography S3 provided no significant independent prognostic information.

Maisel et al. (2011) conducted a secondary analysis of the Collins study (2009) to determine if the strength of the S₃ can provide diagnostic prognostic information in problematic heart failure subgroups. The analysis included dyspneic ED patients older than age 40 who were not on dialysis. A gold standard acute heart failure diagnosis was determined by two cardiologists who were blinded to acoustic cardiography results. In the 995 enrolled patients, S3 strength was a significant prognosticator in univariate analysis for adverse events. When results were incorporated into the multivariable analysis in stepwise fashion, however, it was not as predictive as other variables, such as B-type natriuretic peptide (BNP) values and ST-depression on ECG. In the subgroup of patients with "gray zone" BNP levels, acoustic cardiography increased diagnostic accuracy of acute heart failure (AHF) from 47% to 69%. Acoustic cardiography also improved S₃ detection sensitivity in obese patients compared to auscultation. The authors stated that although acoustic cardiography appears to augment the use of BNP, particularly in problematic subgroups, there were limitations to the study, including the fact that the true diagnostic characteristics when used in real time are unknown, due to the retrospective nature of the study and limited data availability. In addition, cardiologists making the AHF diagnosis were not blinded to BNP results, which would have impacted the diagnosis.

Kobza et al. (2008) conducted a case series (n=57), to evaluate the use of acoustic cardiography using the Audicor device) during electrophysiological (EP) testing for known or suspected cardiac arrhythmias concluding that acoustic cardiography is useful for identifying VT and may facilitate the differential diagnosis of clinically important tachyarrhythmias, particularly when advanced techniques such as EP studies are not available.

Collins et al. (2006) evaluated the use of an S3 heart sound combined with B-type natriuretic peptide (BNP) levels in the diagnosis of emergency room patients with dyspnea (n=439). The author concluded that an S3 sound is highly specific for heart failure and is ideally suited for use in combination with BNP to improve diagnostic accuracy. The sensitivity, specificity, positive and negative predictive value, and diagnostic accuracy of the electronic S3 for primary heart failure were 34%, 93%, 66%, 7%, and 70%, respectively. The values obtained by physician auscultation were 16%, 97%, 84%, 3%, and 66%, respectively. The addition of an Audicor S3 to intermediate BNP levels improved the positive likelihood ratio from 1.3 to 2.9 and improved the positive predictive value from 53% to 80%. The overall ER misdiagnosis rate was 14%. Of the 48 cases, 44 were a failure to diagnose heart failure when it was present. If the Audicor had been used as the sole diagnostic tool among these 44 ultimately considered to have primary HF, 15 would have been correctly diagnosed. Similarly, if the Audicor tool had been used as the sole diagnostic tool, 14 of the 206 patients correctly diagnosed as nonprimary HF would have been incorrectly diagnosed as primary HF. Although the evaluation of S3 heart sounds in combination with BNP testing may improve diagnostic accuracy in patients with dyspnea of unclear etiology, this study does not demonstrate that the Audicor system provides a benefit, when used alone or in combination with other tests, in terms of improved clinical outcomes.

Marcus et al. (2006) conducted a prospective study to determine the diagnostic test characteristics of the S3 and S4 heart sounds for prediction of left ventricular dysfunction using the Audicor system in patients undergoing elective left-sided heart catheterization (n=90). Patients underwent computerized heart sound phonocardiographic analysis (Audicor system) for assessment of S3/S4 heart sounds, cardiac catheterization for assessment of left ventricular end-diastolic pressure (LVEDP), transthoracic echocardiography for evaluation of left ventricular ejection fraction (LVEF), and blood sampling for BNP. Mean LVEDP was significantly elevated; LVEF was reduced; and median BNP was elevated in those with an S3, S4, or both, compared to patients without a diastolic heart sound. The sensitivities of these heart sounds to detect an elevated LVEDP, reduced LVEF, or elevated BNP were 41%, 52%, 32% for an S3, and 46%, 43%, and 40% for an S4, respectively. The authors concluded that neither the phonocardiographic S3 nor the S4 is a sensitive marker of left ventricular dysfunction. The absence of an S3 or S4 using phonocardiographic testing (Audicor system) is therefore not sufficient to exclude ventricular dysfunction. If present, the phonocardiographic S3 and S4 are specific for an elevated LVEDP, depressed LVEF, and elevated BNP level.

Professional Societies/Organizations

American College of Cardiology/American Heart Association (ACC/AHA): ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction (O'Gara, et al., 2013) and the ACC/AHA Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (Yancey, et al., 2013), do not include the use correlated audioelectric cardiography or acoustic heart sounds as a diagnostic tool. In addition, this technology is not mentioned in AHA/ACC Recommendations for the Standardization and Interpretation of the Electrocardiogram, Part I (Kligfield, et al., 2007) and II (Mason, et al., 2007).

American Heart Association (AHA): The AHA scientific statement, Acute Heart Failure Syndromes: Emergency Department Presentation, Treatment, and Disposition: Current Approaches and Future Aims, includes a discussion of focused areas for future investigation. The authors note that the search for additional tools to improve the diagnostic accuracy for patients with undifferentiated dyspnea and possible acute heart failure syndromes remains a high priority. Electronic detection of third heart sounds (S₃) using acoustic cardiography is included among several tools that have been investigated as both stand-alone and adjunct diagnostic measures, but appear to provide little benefit over existing approaches (Weintraub et al., 2010).

Use Outside of the US

Australian and New Zealand Horizon Scanning Network ([ANZHSN], 2010): A Horizon Scanning Technology Prioritizing Summary notes that although comparative evidence indicated that the adjunctive use of acoustic cardiography may be of benefit in the diagnosis of heart failure, the application of this technology in the acute setting was considered impractical.

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Transluminal Peripheral Atherectomy (CPT Codes 0234T, 0235T, 0236T, 0237T, 0238T)

Peripheral artery disease (PAD) broadly encompasses the vascular diseases caused primarily by atherosclerosis and thromboembolic pathophysiologic processes that alter the normal structure and function of the aorta, its visceral arterial branches, and the arteries of the lower extremity (American College of Cardiology Foundation [ACCF]/American Heart Association [AHA], 2011). PAD may be treated medically, and with angioplasty and stenting for patients not responding to medical treatment. Atherectomy involves the removal of plaque burden using physical or ablative means (e.g., laser) in a directional (proximal to distal, usually) or rotational manner and may or may not be combined with angioplasty and stenting (Zaetta, et al. 2017). Atherectomy may be used in the atherectomy of femoral, popliteal artery and tibial, peroneal artery. It has been proposed to be used in the treatment of in arteries above the inguinal ligaments (renal, visceral, abdominal aorta, brachiocephalic trunk and branches and iliac artery).

Literature Review

The medical literature has shown atherectomy to be both safe and effective in femoro-popliteal and infrapopliteal segments. The published peer reviewed scientific literature is preliminary and limited for atherectomy in arteries above the inguinal ligaments (renal, visceral, abdominal aorta, brachiocephalic trunk and branches and iliac artery) and mainly involves small retrospective studies of procedures involving iliac artery.

Valle et al. (2017) reported on a case study of orbital atherectomy in the renal vasculature. A retrospective, uncontrolled, single-center study (Thatipelli, et al., 2009) evaluated the safety and efficacy of blunt microdissection in patients with symptomatic CTOs of the pelvis and lower extremities. Follow-up data were available for up to 1 year. The study included 61 patients who underwent 67 procedures in 86 arteries. The target lesion was located in the aortoiliac artery in 11 of 87 segments (13%), femoropopliteal artery in 72 (83%), and infrapopliteal artery in 4 (5%). All had severe claudication, rest pain, or tissue loss. The authors concluded that this treatment is safe and efficacious, but also noted that the results, drawn from a group of patients referred

to a tertiary center, may not be applicable to the general population of patients with PAD. Furthermore, the follow-up data are incomplete since a high number of cases were not included, which limits the ability to determine the actual rates of treatment success.

Professional Societies/Organizations

American College of Cardiology Foundation/American Heart Association ([ACCF/AHA], 2011): The ACCF/AHA published a guideline titled, Management of Patients with Peripheral Artery Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic), which is adapted from the 2005 ACCF/AHA Guideline and the 2011 ACCF/AHA focused update. Regarding endovascular treatment of claudication the Guideline notes:

- Class IIa, Level of Evidence C recommendation notes that stents (and other adjunctive techniques such as lasers, cutting balloons, atherectomy devices, and thermal devices) can be useful in the femoral, popliteal, and tibial arteries as salvage therapy for a suboptimal or failed result from balloon dilation (e.g., persistent translesional gradient, residual diameter stenosis >50%, or flow limiting dissection).
- Class IIb, Level of Evidence A recommendation notes that the effectiveness of stents, atherectomy, cutting balloons, thermal devices, and lasers for the treatment of femoral-popliteal arterial lesions (except to salvage a suboptimal result from balloon dilation) is not well established.
- Class IIb, level of evidence C recommendation notes that the effectiveness of uncoated/uncovered stents, atherectomy, cutting balloons, thermal devices, and lasers for the treatment of infrapopliteal lesions (except to salvage a suboptimal result from balloon dilation) is not well established."

Definitions regarding class and level of evidence ratings are as follows:

Class IIa, Level of Evidence: A: Benefit >>Risk. Additional studies with focused objectives needed. It is reasonable to perform procedure/administer treatment, recommendation in favor of treatment or procedure being useful/effective, some conflicting evidence from multiple randomized trials or meta-analyses;

Class IIb, Level of Evidence: A: Benefit ≥ Risk. Additional studies with broad objectives needed; additional registry data would be helpful. Procedure/Treatment may be considered. Recommendation's usefulness/efficacy less well established, greater conflicting evidence from multiple randomized trials or meta-analyses;

Class IIb, Level of Evidence: C: Benefit ≥ Risk. Additional studies with broad objectives needed; additional registry data would be helpful. Procedure/Treatment may be considered. Recommendation's usefulness/efficacy less well established. Only diverging expert opinion, case studies, or standard of care.

Use Outside of the US

European Stroke Organisation/European Society of Cardiology (ESC): In a practice guideline on the diagnosis and treatment of peripheral artery diseases, these organizations states that atherectomy devices have unclear long-term benefits and that aortoiliac or bifemoral bypass is usually recommended for diffuse aortoiliac disease. Owing to the limited probability of improvement in symptoms with exercise therapy in the case of aortoiliac lesions, revascularization should be considered without initial conservative treatment. Surgery is limited to extensive lesions without the possibility for endovascular treatment. In patients with disabling intermittent claudication that impacts their activities of daily living, with culprit lesions located at the aorta/iliac arteries, revascularization (endovascular or surgical) should be considered as the first choice therapeutic option. In the external iliac arteries, a primary stenting strategy using self-expandable stents is preferred over provisional stenting, mainly due to a lower risk of dissection and elastic recoil (European Stroke Organisation/ESC 2011).

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Near-Infrared Guidance for Vascular Access Requiring Real-Time Digital Visualization for Evaluation of Potential Access Sites and Vessel Patency (CPT Code 99199)

A peripheral venous catheter is most commonly used for venous access. Traditional techniques for determining the location of a peripheral vein includes palpating the skin, and unaided visualization of the skin in ambient light (Perry, 2011). Use of a near-infrared imaging system has been proposed as an alternative method to aid in visualization of the superficial vasculature. The imaging system provides a display of peripheral vasculature in real-time. It is purported to reduce the number of intravenous (IV) attempts, reduce the time it takes to initiate an IV and improve patient satisfaction (Christie Medical, 2013).

U.S. Food and Drug Administration (FDA): The VTS1000 Liquid Crystal Vein Locator (VueTek Scientific™, LLC, Gray, MN) received 510 (k) approval on Feb 18, 2011. The VTS1000 is a noninvasive electronic device to aid in the visualization of superficial vasculature. According to the 510(k) summary it is indicated for use during procedures requiring vascular or peripheral vascular access.

Literature Review

Rothbart et al. (2015) reported on a retrospective study of that examined the use of Accuvein® AV300 vein viewer used to facilitate venous cannulation in children. The study included 238 consecutive pediatric patients preceding surgical interventions. The subjects were allocated to groups [control group (124 patients) and intervention group (114 patients)] in a non-random way - randomization was not feasible because data was acquired retrospectively. In control group, peripheral IV cannulation was performed without supporting device, in intervention group with support of AV300. Time and number of attempts until successful venous cannulation were defined as primary end points. The study found that the median time until successful cannulation was 2 min (range 0.1-20, quartiles: 25%: 1; 75%: 5) in the intervention group and 1 min (range 0.1-18, quartiles: 25%: 0.2; 75%: 2) in the control group ($p < 0.01$). Median number of attempts was higher in the intervention group (2; range 1-6, quartiles: 25%: 1; 75%: 3) than in the control group (1; range 1-6, quartiles: 25%: 1; 75%: 2, $p < 0.01$). the rate of cannulations successful at first attempt was 0.45 (51 of 114, 95% CI 0.35-0.54) in the intervention group and 0.73 (90 of 124, 95% CI 0.65-0.81) in the control group ($p < 0.01$). the authors concluded that they were not able to reduce neither time nor number of attempts until a successful venous cannulation in children using the vein viewer and that laser-supported cannulation cannot be recommended for standard procedures. The study was limited with the lack of randomization.

Van der Woude et al. (2013) reported results of a pragmatic cluster randomized controlled clinical trial using the Vasculuminator in a population of children with dark skin color requiring intravenous (IV) cannulation in the operating room. Eighty-eight patients were included in the study (control, $n=45$; Vasculuminator, $n=43$). The

availability of the VascuLuminator to anesthesiologists at the operating complex was randomized by computer in clusters of one week. In the VascuLuminator group IV cannulation was aided by the device, whereas the device was not available at the operating room in the control group. Success at first attempt was not significant between the two groups ($p=0.27$). Median time to successful cannulation was not significant between groups ($p=.54$). In the subgroup of children a priori anticipated to be difficult to cannulate (i.e., "hard" or "very hard"), there was a trend to higher success at first attempt in the VascuLuminator group ($p = 0.03$). The authors noted data suggest limited value of the VascuLuminator in facilitating IV cannulation in a subgroup of children with dark skin color who are anticipated to be difficult to cannulate.

Kim et al. (2012) evaluated a group of 111 children who were randomized into one of the two groups (VeinViewer, $n=54$) or control ($n=57$). There was no significant difference in the overall first attempt success rate using the VeinViewer compared with control ($p=0.526$). There was no significant difference between the groups for easy ($p=0.485$), or difficult patients ($p=.026$). Limitations to the study cited by the authors included that the procedural time was analyzed only in patients with successful venous access on the first attempt because the time interval after the first failed attempt varied according to the operator and the situation. Further, the amount of training and practice to attain proficiency with the VeinViewer has not been established.

Phipps et al. (2012) randomized 115 preterm and term neonates undergoing placement of peripherally inserted central catheters by use of VeinViewer ($n=59$) or standard techniques ($n=56$). Overall, there was a trend to more successful placement using VeinViewer, but no statistical significance ($p=0.08$). When analysis was limited to the first attempt at cannulation no differences between the two techniques were found ($p=0.55$). Additionally, infants randomized to the VeinViewer were more mature (30 ± 2 weeks gestational age (GA) versus 28 ± 2 weeks GA; $p=0.08$). Study limitations included lack of blinding regarding use of VeinViewer compared with standard techniques. Larger studies are needed to demonstrate the effectiveness of this device over standard techniques for attaining peripheral venous access.

Chapman et al. (2011) reported results of a prospective, randomized study of children aged 0 to 17 who required nonemergent peripheral intravenous (PIV) catheter placement. Participants were randomized to standard PIV cannulation or PIV cannulation with the VeinViewer (Christie Medical Holdings, Cypress, CA, formerly Luminetx, Memphis, TN). The primary outcome measure was time to PIV placement. Secondary outcome measures included number of PIV attempts and pain scores as reported by the child, parent or guardian and nurse. A total of 323 patients completed the study. No differences in time to PIV placement, number of PIV attempts or pain scores was noted for the overall study group. However, a planned subgroup analysis of children aged 0 to 2 ($n=107$) did yield significant results for time to PIV placement ($p<0.047$), and for nurses' perception of pain ($p=0.01$). Data did not support improvement in outcomes for the total study group. Additional randomized controlled trials (RCT) should be conducted to determine the role of this device for evaluation of potential access sites.

Perry et al. (2011) conducted a prospective RCT to determine whether the use of a near-infrared light venipuncture aid (VeinViewer, Christie Medical Holdings, Cypress, CA, formerly Luminetx, Memphis, TN) would improve the rate of successful first-attempt placement of intravenous (IV) catheters in a high-volume pediatric emergency department (ED). One hundred twenty-three patients were randomized to use of the device ($n=62$) or the traditional technique of palpation of the overlying skin and unaided visualization of peripheral veins for IV access using only ambient room light ($n=61$). If a vein could not be cannulated after three attempts, patients crossed over from one study arm to the other, and study nurses attempted placement with the alternative technique. The primary end point was first-attempt success rate for intravenous (IV) catheter placement. After completion of patient enrollment, a questionnaire was completed by study nurses as a qualitative assessment of the device. There was no significant difference in first-attempt success rate between the standard and device groups. Of the 19 study nurses, 14 completed the questionnaire. Seventy percent expressed neutral or unfavorable assessments of the device in nondehydrated patients. Ninety percent of nurses found the device a helpful tool for patients in whom IV access was difficult. Additional RCTs with large patient populations should be conducted to demonstrate the role of the device in these patients.

Use Outside of the US

No relevant information.

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Intravascular Optical Coherence Tomography (OCT) (Coronary Native Vessel or Graft) (CPT Codes 92978, 92979)

Invasive coronary angiography is considered the gold standard for evaluating patients with suspected myocardial ischemia. Intracoronary optical coherence tomography (OCT) is an intravascular imaging technique performed during cardiac catheterization that measures the echo time delay and intensity of backscattered light from tissue's internal microstructure. This diagnostic procedure creates high-resolution, cross-sectional images of the coronary arteries to permit quantification of lumen dimensions and the extent of lumen narrowing, visualization of atherosclerotic plaque, and characterization of the structure and extent of plaque.

OCT systems comprise a fiberoptic imaging catheter attached to a patient interface unit, which connects to a system console. The console contains an optical engine (i.e., light source, beam splitter, reference arm, detectors, signal processor) and a computer that collects multiple light signals reflected from different tissue depths and combines them to make a three-dimensional image. Signal intensity is mapped to a color space that is displayed on a monitor.

OCT is frequently compared to intravascular ultrasound (IVUS). Compared to IVUS, it is purported that OCT provides enhanced contrast between lumen and vessel walls, higher axial resolution of intracoronary plaque structures, and faster pullback. OCT catheters are smaller in diameter than IVUS catheters, allowing safer image acquisition from smaller-caliber vessels (St. Jude Medical, 2012).

The major limitation of OCT is its inability to consistently image the outer layer of the vessel wall and assess plaque burden due to limited tissue penetration (1.0 to 1.5 mm). Also, using OCT to measure large-diameter vessels at proximal target sites may be difficult, and the manufacturer has indicated that aorto-ostial lesions are not suitable for OCT imaging.

U.S. Food and Drug Administration (FDA): Several intracoronary optical coherence tomography products made by St. Jude Medical, Inc., (St. Paul, MN), have received FDA 510 (k) approval. These include the C7 XR Imaging system (April 2010) and the C7 Dragonfly Intravascular Imaging catheter and disposable accessories (April, 2010). Others include the ILUMIEN System, (LightLab Imaging, Inc., Westford, MA; July 2011) and the OCT Imaging system and catheter (Volcano Corporation (San Diego, CA) received 510(k) approval on Jan, 2010).

Literature Review

Although there are a number of prospective and retrospective studies and review articles in the published peer-reviewed scientific literature, randomized controlled trial data are lacking to inform health outcomes as a result of intracoronary optical coherence tomography. A number of clinical trials are ongoing.

Ali et al (2016) reported on a randomized controlled trial that examined whether or not a novel OCT-based stent sizing strategy would result in a minimum stent area similar to or better than that achieved with IVUS guidance and better than that achieved with angiography guidance alone. The primary efficacy endpoint was post-PCI minimum stent area, measured by OCT at a masked independent core laboratory at completion of enrolment, in all randomly allocated participants who had primary outcome data. The primary safety endpoint was procedural major adverse cardiovascular events (MACE). The study randomly allocated 450 patients (158 [35%] to OCT, 146 [32%] to IVUS, and 146 [32%] to angiography), with 415 final OCT acquisitions analyzed for the primary endpoint (140 [34%] in the OCT group, 135 [33%] in the IVUS group, and 140 [34%] in the angiography group). The final median minimum stent area was 5.79 mm² (IQR 4.54-7.34) with OCT guidance, 5.89 mm² (4.67-7.80) with IVUS guidance, and 5.49 mm² (4.39-6.59) with angiography guidance. OCT guidance was non-inferior to IVUS guidance (one-sided 97.5% lower CI -0.70 mm²; p=0.001), but not superior (p=0.42). OCT guidance was also not superior to angiography guidance (p=0.12). Procedural MACE was noted in four (3%) of 158 patients in the OCT group, one (1%) of 146 in the IVUS group, and one (1%) of 146 in the angiography group (OCT vs IVUS p=0.37; OCT vs angiography p=0.37). The authors concluded that OCT using a specific reference segment external elastic lamina-based stent optimization strategy was safe and resulted in similar minimum stent area to that of IVUS-guided PCI, however the results warrants a large-scale randomized trial to establish whether or not OCT guidance results in superior clinical outcomes to angiography guidance.

Meneveau et al. (2016) reported on a multicenter, randomized study involving 240 patients with non-ST-segment elevation acute coronary syndromes to compare OCT-guided PCI (use of OCT pre- and post-PCI; OCT-guided group) to fluoroscopy-guided PCI (angiography-guided group). The primary end point was the functional result of PCI assessed by the measure of post PCI fractional flow reserve. The secondary end points included procedural complications and type 4a peri-procedural myocardial infarction and safety was assessed by the rate of acute kidney injury. Findings included that OCT use led to a change in procedural strategy in 50% of the patients in the OCT-guided group. The primary end point was improved in the OCT-guided group, with a significantly higher fractional flow reserve value (0.94±0.04 versus 0.92±0.05, P=0.005) compared with the angiography-guided group. There was no significant difference in the rate of type 4a myocardial infarction (33% in the OCT-group versus 40% in the angiography-guided group, P=0.28). The rates of procedural complications (5.8%) and acute kidney injury (1.6%) were identical in each group despite longer procedure time and use of more contrast medium in the OCT-guided group. Post-PCI OCT revealed stent under-expansion in 42% of patients, stent malapposition in 32%, incomplete lesion coverage in 20%, and edge dissection in 37.5%. This led to the more frequent use of post-stent overdilation in the OCT-guided group versus the angiography-guided group (43% versus 12.5%, P<0.0001) with lower residual stenosis (7.0±4.3% versus 8.7±6.3%, P=0.01). The authors concluded that in patients with non-ST-segment elevation acute coronary syndromes, OCT-guided PCI is associated with higher post-procedure fractional flow reserve than PCI guided by angiography alone. The procedure did result in longer procedure time, but did not increase peri-procedural complications, type 4a myocardial infarction, or acute kidney injury.

Hayes published a directory report for optical coherence tomography (OCT) for plaque characterization and stent implantation (Hayes, 2016). The review included 19 studies, including 8 prospective and 5 retrospective uncontrolled or noncomparative cohort studies; one retrospective comparative cohort study; one prospective, case-matched cohort study; two retrospective, case-matched cohort or cross-sectional studies; and two randomized controlled trials (RCTs). The review noted that reviewed studies provide consistent evidence that OCT can detect features of plaques and stents that are associated with increased risk of adverse cardiac events. However, the reviewed studies do not provide sufficient evidence to conclude that the information obtained with OCT can be used to improve patient management and reduce the risk associated with adverse plaque and stent characteristics, particularly relative to guidance of percutaneous coronary interventions (PCI) with intravascular ultrasonography (IVUS). Additional well-designed studies are needed to determine whether guidance of PCI with OCT and angiography improves patient outcomes versus guidance with IVUS and angiography or with angiography alone.

Professional Societies/Organizations

American College of Cardiology Foundation, American Heart Association, and Society for Cardiovascular Angiography and Interventions Association Task Force: These Societies published a joint practice guideline titled, Percutaneous Coronary Intervention (Levine, et al., 2011). The guideline notes that

compared with IVUS, optical coherence tomography has greater resolution (10 to 20 micronmeter axially) but more limited depth of imaging (1 to 1.5 mm). Unlike IVUS, optical coherence tomography requires that the artery be perfused with saline solution or crystalloid during image acquisition and therefore does not permit imaging of ostial lesions. Clinical studies have shown low optical coherence tomography complication rates, similar to those of IVUS. The excellent resolution of optical coherence tomography permits detailed in vivo 2-dimensional imaging of plaque morphological characteristics (e.g., calcification, lipid, thrombus, fibrous cap thickness, and plaque ulceration or rupture) and evaluation of the arterial response to stent implantation (e.g., stent strut neointimal thickness and apposition) and may be of value in clinical research. The practice guideline notes the appropriate role for optical coherence tomography in routine clinical decision making has not been established.

Use Outside of the US

The Task Force on Myocardial Revascularization of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery: These Societies published joint Guidelines on Myocardial Revascularization in 2010. These guidelines note that OCT is a light-based modality of intravascular imaging with higher spatial resolution than intravascular ultrasound (15µm vs. 100µm). Its penetration is lower than intravascular ultrasound but it provides detailed imaging of the endoluminal borders. At present, OCT is a valuable research tool.

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Endothelial Function Assessment (CPT Code 0337T)

The endothelium helps to regulate vascular tone, cellular adhesion, thromboresistance, smooth muscle cell proliferation, and vessel wall inflammation. Alteration in endothelial function precedes the development of morphological atherosclerotic changes and can also contribute to lesion development and later clinical complications (Deanfield, 2007). Noninvasive endothelial function assessment has been proposed as a means to predict the risk of atherosclerosis and cardiovascular disease.

One method involves measurement of the brachial diameter before and after an increase in shear stress induced by reactive hyperemia or flow-mediated dilation (FMD). Special probes that have pneumoelectrical tubing that connect to a computer are placed in an arm stabilizer and the index finger is placed in a probe. A

sphygmomanometer cuff is placed on the forearm distal to the brachial artery, inflated and released for a timed period. This is repeated with higher pressures used to mimic occlusion. Finally the pressures are measured five minutes after the pressure is released. FMD occurs as a result of local endothelial release of nitrous oxide. The information is evaluated by proprietary software and a score indicating the endothelial health is generated. Digital peripheral arterial tonometry (PAT) quantifies reactive hyperemia-induced changes in pulse volume amplitude (PVA) in the finger tip, and is an automated method to non-invasively assess endothelial function (Lee, 2012). According to the manufacturer, EndoPAT™ measures several vascular beds, composed of small vessels and microcirculation. The manufacturer also notes the EndoPAT™ corrects for systemic changes by a simultaneous measurement from the (un-occluded) contra-lateral arm.

U.S. Food and Drug Administration (FDA): The Endo PAT 2000 device (Itamar Medical, Inc., Framingham, MA) received 510(k) approval in November 2003. According to the approval summary it is a non-invasive device, intended for use as a diagnostic aid in the detection of coronary artery endothelial dysfunction (positive or negative) using a reactive hyperemia procedure. The summary also notes "The Endo PAT 2000 has been shown to be predictive of coronary artery endothelial dysfunction in the following patient population: patients with signs or symptoms of ischemic heart disease, who are indicated for coronary artery angiography, but who lack angiographic evidence of obstructive coronary artery disease. The device is intended to be used in a hospital or clinic environment by competent health professionals. The Endo PAT 2000 device is not intended for use as a screening test in the general patient population. It is intended to supplement, not substitute, the physician's decision-making process. It should be used in conjunction with knowledge of the patient's history and other clinical findings."

The CVProfilor® System, Cardiovascular Profiling System, original applicant Hypertension Diagnostics, Inc. (Eagan, MN) received 510(k) approval (K001948) from the FDA in November, 2000 as a Class II device for the noninvasive measurement of blood pressure and pulse rate. According to the summary "It is classified as a noninvasive blood pressure measurement system providing a signal from which systolic, diastolic, mean, or any combination of the three pressures can be derived through the use of transducers placed on the surface of the body."

Literature Review

Randomized controlled clinical trial data are lacking to demonstrate the clinical utility and effectiveness of endothelial function assessment to predict cardiovascular risk. The majority of studies in the published peer-reviewed literature are prospective cohorts.

Hayes published a technology directory report on peripheral arterial tonometry (PAT), a noninvasive device intended for the evaluation of endothelial dysfunction using indirect measurement of induced reactive hyperemia (RH) (Hayes, 2014; 2015; 2016). The review included ten peer-reviewed cross-sectional or prospective cohort studies evaluating RH-PAT, with sample size of 60 to 238 patients. Six studies investigated RH-PAT for: detecting coronary endothelial dysfunction in patients without CAD (one study), for detecting myocardial ischemia in a RH-PAT exercise test (one study), and for detecting or characterizing CAD (four studies). Four studies investigated RH-PAT for predicting cardiovascular adverse events following a surgical procedure. The results varied across studies and applications due to heterogeneity in patient selection criteria, applications, reference standards, and cut-off values. There were no studies evaluating the impact of the use of RH-PAT on health outcomes. The report concluded that evidence evaluating the clinical validity of reactive hyperemia peripheral arterial tonometry is insufficient to determine its value in the evaluation of coronary artery disease or to predict cardiovascular adverse events.

van den Heuvel et al. (2017) reported on a study of 93 patients to examine the applicability of PAT to detect a low risk of coronary artery disease (CAD) in a chest pain clinic. PAT was performed resulting in reactive hyperaemia (RHI) and augmentation (AIx) indices. Patients were risk classified according to HeartScore, Diamond and Forrester pretest probability (DF), exercise testing (X-ECG), and computed tomography calcium scoring (CCS) and angiography (CTA). Correlations, risk group differences and prediction of revascularisation within 1 year were calculated. The results indicated that PAT cannot detect a low risk of CAD, possibly because RHI and AIx versus X-ECG, CCS and CTA represent independent processes.

To assess whether endothelial dysfunction, as detected by peripheral artery tonometry, can predict late cardiovascular events, Rubinshtein et al. (2010) induced reactive hyperemia (RH) following upper arm occlusion of systolic blood pressure in 270 outpatients. The natural logarithmic scaled RH index (L_RHI) was calculated from the ratio between the digital pulse volume during RH and at baseline. Follow-up was seven years. Seven-year adverse event rate was 48% in patients with L_RHI < 0.4 vs. 28% in those with L_RHI ≥ 0.4 (p=0.03). Univariate predictors of adverse events were LRHI, advancing age, and prior coronary bypass surgery. Multivariate analysis identified L_RHI < 0.4 as an independent predictor of AE (p=0.03). Study limitations include an uncontrolled study design, and dropout rate of 17%.

Hamburg et al. (2008) reported results of a correlational cohort study of Framingham Third generation Cohort participants (n=1957). A fingertip peripheral arterial tonometry (PAT) device was used to measure digital pulse amplitude. Measurements were taken at baseline and in 30 second intervals for four minutes during reactive hyperemia induced by five minute forearm cuff occlusion. The relation of PAT ratio to cardiovascular risk factors was strongest in the 90-120 second postdeflation interval (overall model R²=0.159). To determine the relation between the hyperemic response over time following cuff deflation and clinical cardiovascular risk factors, stepwise regression models were performed for the PAT ratio for each 30 second interval with age and sex forced in, selecting from systolic blood pressure, diastolic blood pressure, heart rate, body mass index, total/HDL cholesterol, triglycerides, glucose, diabetes, current smoking, hormone replacement therapy, hypertension treatment, lipid-lowering treatment, and prevalent cardiovascular disease. The relation of PAT ratio to cardiovascular risk factors was strongest in the 90-120 second postdeflation interval (overall model R²=0.159). The authors note study findings support further investigations to define clinical utility and predictive value of digital pulse amplitude. The study was limited by uncontrolled design.

Professional Societies/Organizations

American College of Cardiology Foundation/American Heart Association (ACCF/AHA): These organizations published the 2010 Guideline for the Assessment of Cardiovascular Risk in Asymptomatic Adults. The guideline notes that it is unclear whether these measures of peripheral endothelial health provide incremental predictive information when controlling for traditional risk factors. The guideline further notes that due to the limited data available, the writing committee concluded that it was premature to recommend serial FMD measurements to monitor treatment effects. In addition, due to the technical challenges of standardizing measurement of FMD and the relatively modest evidence of incremental change in risk assessment, measurement for risk assessment was not regarded as appropriate for risk assessment in the asymptomatic adult.

American Society of Echocardiography/Society for Vascular Medicine: These societies (Roman, et al., 2006) published a report regarding the clinical application of noninvasive vascular ultrasound in cardiovascular risk stratification. The report notes that the ability of flow-mediated endothelium-dependent brachial artery dilation to provide prognostic information in individuals at intermediate- or low-risk, independent of more standard risk-profiling approaches, remains to be identified.

Use Outside of the US

No relevant information.

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Coding/Billing Information Cardiovascular

Note: 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Cardiovascular Services Considered Experimental/Investigational/Unproven:

| CPT® Codes | Description | Comment |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| <u>33340</u> | Percutaneous transcatheter closure of the left atrial appendage with endocardial implant, including fluoroscopy, transseptal puncture, catheter placement(s), left atrial angiography, left atrial appendage angiography, when performed, and radiological supervision and interpretation | |
| 34806 | Transcatheter placement of wireless physiologic sensor in aneurysmal sac during endovascular repair, including radiological supervision and interpretation, instrument calibration, and collection of pressure data (List separately in addition to code for primary procedure) (Code deleted 12/31/2017) | |
| <u>34839</u> | Physician planning of a patient-specific fenestrated visceral aortic endograft requiring a minimum of 90 minutes of physician time | |
| <u>34841</u> | Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including one visceral artery endoprosthesis (superior mesenteric, celiac or renal artery) | |
| <u>34842</u> | Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including two visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s]) | |
| <u>34843</u> | Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including three visceral artery | |

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|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | endoprostheses (superior mesenteric, celiac and/or renal artery[s]) | |
| <u>34844</u> | Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including four or more visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s]) | |
| <u>34845</u> | Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including one visceral artery endoprosthesis (superior mesenteric, celiac or renal artery) | |
| <u>34846</u> | Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including two visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s]) | |
| <u>34847</u> | Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including three visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s]) | |
| <u>34848</u> | Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including four or more visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s]) | |
| <u>92978</u> | Endoluminal imaging of coronary vessel or graft using intravascular (IVUS) or optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; initial vessel (List separately in addition to code for primary procedure) | Considered Experimental/Investigational/Unproven when used to report CPT code 92978 using endoluminal imaging of coronary vessel or graft using optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; initial vessel |

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| <u>92979</u> | Endoluminal imaging of coronary vessel or graft using intravascular (IVUS) or optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; each additional vessel (List separately in addition to code for primary procedure) | Considered Experimental/Investigational/Unproven when used to report CPT code 92979 using endoluminal imaging of coronary vessel or graft using optical coherence tomography (OCT) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation and report; each additional vessel |
| <u>93799</u> | Unlisted cardiovascular service or procedure | Considered Experimental/Investigational/Unproven when used to report acoustic cardiography |
| <u>93982</u> | Noninvasive physiologic study of implanted wireless pressure sensor in aneurysmal sac following endovascular repair, complete study including recording, analysis of pressure and waveform tracings, interpretation and report (Code deleted 12/31/2017) | |
| <u>99199</u> | Unlisted special service, procedure or report | Considered Experimental/Investigational/Unproven when used to report near-infrared guidance for vascular access requiring real-time digital visualization of subcutaneous vasculature for evaluation of potential access sites and vessel patency |
| <u>0205T</u> | Intravascular catheter-based coronary vessel or graft spectroscopy (eg, infrared) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation, and report, each vessel (List separately in addition to primary procedure) | |
| <u>0234T</u> | Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; renal artery | |
| <u>0235T</u> | Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; visceral artery (except renal), each vessel | |
| <u>0236T</u> | Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; abdominal aorta | |
| <u>0237T</u> | Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; brachiocephalic trunk and branches, each vessel | |
| <u>0238T</u> | Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; iliac artery, each vessel | |
| <u>0254T</u> | Endovascular repair of iliac artery bifurcation (eg, aneurysm, pseudoaneurysm, arteriovenous malformation, trauma, dissection) | |

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| | using bifurcated endograft from the common iliac artery into both the external and internal iliac artery, including all selective and/or nonselective catheterization(s) required for device placement and all associated radiological supervision and interpretation, unilateral | |
| <u>0255T</u> | Endovascular repair of iliac artery bifurcation (eg, aneurysm, pseudoaneurysm, arteriovenous malformation, trauma) using bifurcated endoprosthesis from the common iliac artery into both the external and internal iliac artery, unilateral; radiological supervision and interpretation (Code deleted 12/31/2017) | |
| <u>0266T</u> | Implantation or replacement of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intraoperative interrogation, programming, and repositioning, when performed) | |
| <u>0267T</u> | Implantation or replacement of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming and repositioning, when performed) | |
| <u>0268T</u> | Implantation or replacement of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed) | |
| <u>0269T</u> | Revision or removal of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed) | |
| <u>0270T</u> | Revision or removal of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed) | |
| <u>0271T</u> | Revision or removal of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed) | |
| <u>0272T</u> | Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (eg, battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day); | |
| <u>0273T</u> | Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (eg, battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day); with programming | |
| <u>0337T</u> | Endothelial function assessment, using peripheral vascular response to reactive hyperemia, non-invasive (eg, brachial artery ultrasound, peripheral artery tonometry), unilateral or bilateral | |

| HCPCS Codes | Description |
|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <u>C2624</u> | Implantable wireless pulmonary artery pressure sensor with delivery catheter, including all system components |
| <u>C9741</u> | Right heart catheterization with implantation of wireless pressure sensor in the pulmonary artery, including any type of measurement, angiography, imaging supervision, interpretation, and report |

*Current Procedural Terminology (CPT®) ©2017 American Medical Association: Chicago, IL.

Pulmonary

Computer-Aided Detection of Chest Radiographs (CPT Codes 0174T, 0175T)

Computer-aided detection (CAD) systems for computed tomography or digital chest x-rays are software programs that subtract one lung from another to reveal subtle asymmetric opacities, and perform temporal subtraction of prior imaging from the current exam. The basic concept of computer-aided detection (CAD) is to provide computerized image recognition to assist and improve radiologist's interpretation. Through algorithms, CAD technology provides radiologists with regions of interest (ROI) for their interpretation. Although CAD is used most often in mammography, many different types of CAD technologies and/or devices are being developed for detection of various lesions in medical imaging, including conventional x-ray, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound.

Proponents of computer-aided detection with chest x-ray state that diagnostic accuracy is improved with the use of a CAD program and that CAD can expedite screening of at-risk individuals at an earlier and more curable stage of lung cancer. Potential risks of using CAD with chest x-rays may include the generation of false-positive and false-negative results leading to over- and under-diagnosis. Abnormalities (e.g., scars from smoking, areas of inflammation, or other noncancerous conditions) can mimic lung cancer on x-ray. Subsequent additional testing may cause anxiety for the patient or may lead to unnecessary biopsy or surgery and increase medical costs. Also, the use of CAD programs in screening for lung cancer may detect small tumors that would never become life-threatening, putting a patient at risk for unnecessary treatments for cancer, such as chemotherapy or radiation.

U.S. Food and Drug Administration (FDA)

Deus Technologies received FDA premarket approval for its RapidScreen™ CAD system in July 2001. Its intended use is "to identify and mark regions of interest on digital or digitized frontal chest radiographs. It identifies features associated with solitary pulmonary nodules from 9–30 millimeters (mm) in size, which could represent early-stage lung cancer. The device is intended for use as an aid only after the physician has performed an initial interpretation of the radiograph. The device is of little value when used for patients who are not at high risk for lung cancer."

In 2007, Deus Technologies manufacturer Riverain Medical Group (Miamisburg, OH) received approval for a new trade name. The device, as modified, will be marketed under the trade name OnGuard™ and is indicated "to identify and mark ROIs on frontal chest radiographic films from adult males with an increased risk for lung cancer to bring ROI to the attention of the radiologist after the initial reading has been completed. Thus the system assists the radiologist in minimizing observational oversights by identifying areas on the original chest films that may warrant a second review." In March of 2012, Riverain's OnGuard software was renamed ClearRead Detect™. Currently, Riverain Medical's ClearRead Detect™ CAD System is the only FDA-approved CAD systems with a Product Device Description of "Analyzer, Medical Image" for chest x-rays (Product Code MYN). Other CAD systems (for example, mammography or lung computed tomography) are listed under this same device description.

The FDA approved EDDA Technology's (Princeton Junction, NJ) "IQQA® Chest Software Package" in October 2004 under the Product Device Description of Picture Archiving and Communications System (PACS). It uses a real-time interactive pulmonary nodule analysis system for chest digital radiographic image softcopy reading. Intended use states it is "used during the review of digital chest radiographic images. Combining image viewing, evaluation and reporting tools, the software is designed to support the physician in the identification of lung lesions (e.g. nodules), as well as the confirmation, evaluation and documentation of such physician-identified lesions. The IQQA-Chest software package supports a workflow based on automated segmentation for the visual identification of possible lesions. The tools also allow for regional analysis of possible lesions in terms of size, shape and position, thus aiding the physician in the characterization of physician-identified suspicious lesions." Philips Medical Systems (Hamburg, Germany) has licensed EDDA Technology's IQQA® Chest software and markets it under the name xLNA (x-ray lung node assessment) Enterprise.

Literature Review

There is insufficient evidence in the published, peer-reviewed scientific literature addressing the accuracy and clinical utility of CAD of chest x-rays. Well-designed clinical trials are lacking. Studies are primarily retrospective analyses of registry data and there is concern regarding unacceptable false-positive rates. Retrospective registry studies address multiple variables that may impact accuracy such as the experience and training of radiologist using the CAD program, type of chest x-ray utilized (e.g., temporal subtraction, dual energy subtraction) and region of interest identification parameters in the algorithms themselves (e.g., nodules size, bone suppression, and nodule-in-center or nodule-in-circle criterion). Additionally, screening populations and timing for the use of CAD in the diagnostic work-up vary in studies. The clinical utility of CAD of chest x-rays for lung cancer screening is not established. The FDA wording regarding RapidScreen™ CAD systems notes that the device is of little value when used for patients who are not at high risk for lung cancer (Dellios, et al., (2017); Kligerman, et al., 2013; De Boo, et al., 2011; Mezziane, et al., 2012; Szucs-Farkas, et al., 2010; Balkman, et al., 2010; Moore, et al., 2010; White, et al., 2009; Li, et al., 2008; Van Beek, et al., 2008; Bley, et al., 2008; Kakeda, et al., 2004).

Professional Societies/Organizations

American College of Radiology (ACR): ACR (Mohammed, et al., 2013) published appropriateness criteria for the screening of pulmonary metastases. According to the ACR, computer-aided detection (CAD) for pulmonary metastatic disease has been adapted to chest CT. Although these programs are in their developmental phases, the ACR notes it has been suggested that CAD can be used as a second look after the radiologist has completed reviewing the study. However, the ACR notes these applications require more development and can only be used when there is limited breathing artifact and stable lung expansion. CAD is still in the investigative phase and has limited use in evaluating patients with pulmonary metastatic disease.

Use Outside of the US

No relevant information.

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Intermittant and Continuous Measurement of Wheeze Rate for Bronchodilator or Bronchial Challenge (CPT code 94799)

The American Thoracic Society Committee on Pulmonary Nomenclature defines wheezing as high-pitched (dominant frequency of ≥ 400 Hz) continuous adventitial lung sounds (i.e., >250 msec) (Schraufnagel and Murray, 2010). The sound is generated by turbulence in larger airways that collapse with forced expiration (Boat and Green, 2011). Repeated examination may be required to verify a history of wheezing and should be directed toward assessing air movement, ventilatory adequacy, and evidence of chronic lung disease (Boat and Green, 2011). Computerized lung sound analysis involves recording the patient's lung sounds via an electronic device, followed by computer analysis and classification of lung sounds based on specific signal characteristics. Intermittant measurement of wheeze rate by pulmonary sound analysis has been proposed for use in bronchodilator or bronchial challenge diagnostic evaluation. Continuous measurement of wheeze rate by sound analysis has been proposed during treatment assessment such as bronchodilator or bronchial challenge evaluations, and during sleep for documentation of nocturnal wheeze and cough.

U.S. Food and Drug Administration (FDA)

Several devices have received FDA approval for the measurement of wheeze rate. The PulmoTrack™ 2020 System (iSonea, formerly KarmelSoniz, Binyamina, IS, US office: Alta Loma, CA) received 510(k) approval in March 2011. The approval summary notes "The PulmoTrack™ 2020 is intended for the analysis, interpretation and documentation of lung sounds. The PulmoTrack™ 2020 is indicated for use by or under the supervision of a physician while carrying out a provocation test, administering a bronchodilator or performing a physical examination in pulmonary function testing environment when there is a need for performing an acoustic pulmonary function measurement that quantifies the presence of wheezing. It is also indicated when there is a need to listen to amplified and filtered breath sounds. The PulmoTrack™ 2020 is indicated for patient population above two years old." The WIM-PC received 510(k) approval in November 2007. The FDA summary notes "The WIM-PC is intended for the analysis, interpretation and documentation of lung sounds."

Literature Review

Randomized controlled clinical trial data in the published peer-reviewed scientific literature are scarce to inform the effectiveness and clinical utility of wheeze rate measurement. Gurung et al. (2011) performed a systematic review and meta-analysis to estimate the sensitivity and specificity of computerized lung sound analysis for the detection of lung sounds. Eight studies were selected for review. Overall sensitivity for the detection of wheezes or crackles was 88%, and specificity was 85%. The authors noted there is a lack of standardization across studies in the methods used for lung sound recording, computer algorithms for signal analysis and statistical methods for outcome analysis. Further research is needed to address the effectiveness of specific combinations of electronic devices and computing algorithms in clinical and community settings.

Beck et al. (2007) evaluated the use of computerized quantification of wheezing and crackles compared to a clinical score in assessing the effect of inhaled albuterol or inhaled epinephrine in infants with RSV bronchiolitis

during a double blind, randomized, controlled nebulized treatment pilot study. Computerized quantification of wheezing and crackles (PulmoTrack) and a clinical score were performed prior to, 10 minutes post and 30 minutes post treatment. Breath segments containing at least five consecutive interference-free breaths were analyzed for a total of 20 breaths. Wheeze Rate (percent of time wheezing of total breath time) and crackle count (number of crackles per breath) were determined by the PulmoTrack® for each breath cycle, and averaged over the 20 breaths. Satisfactory lung sounds recording and analysis was achieved in all subjects. There was no significant change in objective quantification of wheezes and crackles or in the total clinical scores either within the groups or between the groups. Although data suggest that automated wheeze rate measurement is feasible, the authors note that a larger study is necessary to assess the correlation between the computerized crackle and wheeze counts and the Clinical Score in response to treatment in RSV bronchiolitis.

Use Outside of the US

No relevant information.

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Cryoablation of Lung Tumors (CPT Code 0340T, 32994) (Code 0340T deleted 12/31/2017; use 32994 to report)

Pulmonary tumor cryoablation involves the destruction of tumor tissue using extreme cold. This is also known as cryoablation, cryosurgery, or cryotherapy. In this procedure a small thin wand-like needle, known as a cryoprobe, is inserted through the skin of the chest and between the ribs. Under computerized tomography (CT) guidance, the probe is advanced into the lesion of the lung and any tumor extensions to the pleura and/or chest wall. Compressed argon gas is passed through the probe and into the tumor, which freezes it and destroys the tissue. Treatment with the probe usually takes several minutes and may include repositioning the probe within the lesion so that overlapping ablations treat the entire tumor.

Literature Review

Randomized controlled clinical trial data are lacking in the published peer-reviewed scientific literature to demonstrate the safety and effectiveness of pulmonary tumor ablation by cryoablation. Studies are limited by uncontrolled design and small patient populations. Additional well-designed high quality studies are necessary to inform on health outcomes. Further, published professional consensus is necessary before this treatment can be translated into routine clinical practice.

Moore et al. (2015) reported on a retrospective study that evaluated long-term survival in 45 patients with early stage non-small cell lung cancer (NSCLC) treated with cryoablation treatment. The study findings included five year survival rate 67.8% ± 15.3; the cancer-specific survival rate was 56.6% ± 16.5; and the 5-year progression-free survival rate was 87.9% ± 9. The combined local and regional recurrence rate was 36.2%. Major

complications occurred 6.4% of patients that included two cases of hemoptysis and a prolonged placement of a chest tube requiring mechanical sclerosis in one patient. There were no deaths in the first 30 days after treatment.

Hayes published a technology directory report regarding cryoablation for treatment of non-small cell lung cancer (NSCLC) (Hayes, 2015; 2017). The review included one randomized controlled trial (RCT), six nonrandomized comparative studies, and one uncontrolled study, with sample size of 36 to 346 patients. The body of evidence concerning cryoablation for NSCLC is moderate in size and low in overall quality. Results of the available studies provide preliminary evidence that cryoablation is a reasonably safe and effective treatment for NSCLC. While the results of some of the studies were somewhat conflicting or inconclusive, there is some evidence of improved survival when cryoablation is used alone or with other therapies. Additional well-designed studies with long-term follow-up are needed to define the clinical role of cryoablation relative to other common therapies for NSCLC such as surgery, RFA, chemotherapy, radiation therapy, and immunotherapy.

Yashiro et al. (2013) reported results of a prospective study of 71 consecutive patients with 210 pulmonary tumors treated with 102 sessions of percutaneous cryoablation of lung tumors. A mean of 1.4 sessions was performed per case. A maximum of four cryoprobes was used on one lesion; the number and diameter of the probes were based on estimated tumor size. Every procedure was performed using a triple freeze/thaw protocol. High-pressure argon gas was used for freezing. There was no procedural mortality. Of 210 tumors, technical success was achieved for 167 (79.5%). At a median follow-up of 454 days, local progression occurred in 50 tumors (23.8%). One-, 2-, and 3-year local progression-free rates were 80.4%, 69.0%, and 67.7%, respectively, and technique effectiveness rates were 91.4%, 83.0%, and 83.0%, respectively. Existence of a thick vessel (diameter ≥ 3 mm) no more than 3 mm from the edge of the tumor was assessed as an independent factor (HR, 3.84; 95% CI, 1.59–9.30; $P = .003$) associated with local progression by multivariate analysis. Although results are promising, study limitations include uncontrolled design, and small patient numbers.

Kawamura et al. (2006) conducted a nonrandomized uncontrolled study to evaluate cryoablation of 35 pulmonary metastatic tumors in 20 patients who were not surgical candidates. In all cases cryoablation was performed percutaneously under CT guidance with local anesthesia. A total of 22 sessions of cryoablation were performed. Pneumothorax occurred in 11 of the 22 sessions, primarily after the completion of the ablation procedure. A chest tube was inserted in one case, transient needle aspiration was performed in three cases, and in seven cases no additional treatment was given. Phrenic nerve palsy occurred during one session. Mean hospital stay after treatment was 2.6 days, although for the initial five sessions, it was 5.4 days. There were no treatment-related deaths or conversion to surgical intervention. The follow-up period was 9 to 28 months. Local recurrence occurred in 7 (20%) of tumors. Five patients underwent repeat cryoablation without complications. Study limitations which preclude the ability to apply results to other populations include uncontrolled randomized design and small study populations.

Professional Societies/Organizations

National Comprehensive Cancer Network™ (NCCN™): The NCCN (2017) guidelines do not contain detailed information on cryoablation for NSCLC. Cryotherapy is briefly mentioned as follows (NCCN, 2017):

- Resection is the preferred local treatment modality (other modalities include radiotherapy ablation, cryotherapy, and stereotactic ablative radiotherapy).

Use Outside of the US

European Society for Medical Oncology (ESMO): ESMO published clinical practice guidelines for metastatic non-small cell lung cancer (Novello, et al., 2016). The guidelines note that in case of symptomatic major airways obstruction or postobstructive infection, endoscopy debulking by laser, cryotherapy or stent placement may be helpful (III, C).

Levels of evidence and grades of recommendation

III Prospective cohort studies

C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs), optional

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Coding/Billing Information Pulmonary

Note: 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Pulmonary Services Considered Experimental/Investigational/Unproven:

| CPT® Codes | Description | Comment |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <u>32994</u> | Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging guidance when performed, unilateral; cryoablation | |
| <u>94799</u> | Unlisted pulmonary service or procedure | Considered Experimental/Investigational/Unproven when used to report intermittent measurement of wheeze rate for bronchodilator or bronchial challenge diagnostic evaluation |
| <u>0174T</u> | Computer aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed concurrent with primary interpretation (List separately in addition to code for primary procedure) | |
| <u>0175T</u> | Computer aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed remote from primary interpretation | |
| <u>0340T</u> | Ablation, pulmonary tumor(s), including pleura or chest wall when involved by tumor extension, percutaneous, cryoablation, unilateral, includes imaging guidance (Code deleted 12/31/2017) | |

***Current Procedural Terminology (CPT®) ©2017 American Medical Association: Chicago, IL.**

Gastroenterology

Fecal Calprotectin Testing (FC) (CPT Code 83993)

This laboratory test measures the level of calprotectin in stool. Calprotectin is a calcium and zinc binding protein that is found predominantly in neutrophils. The concentration of calprotectin is higher in feces compared to plasma and can be measured by enzyme-linked immunosorbent assay (ELISA) using less than five grams of stool. Although the normal range has been defined for FC, an optimal cutoff point for distinguishing inflammatory bowel disease (IBD) from other diagnoses has not been defined (von Roon et al. 2007). It has been studied as a surrogate marker of intestinal inflammation in inflammatory bowel diseases (e.g., Crohn's disease, ulcerative colitis), colorectal cancer, diverticular disease, and polyposis of the colon. It has also been studied as a marker to predict response to treatment and relapse of disease.

U.S. Food and Drug Administration (FDA)

PhiCal™ Fecal Calprotectin Immunoassay (Genova Diagnostics, Inc., Ashville, NC) received Class II device approval in 2006. The immunoassay is a lab test that measures the amount of fecal calprotectin in a patient's stool sample. The PhiCal test is indicated for use as an in vitro diagnostic to aid in the diagnosis of inflammatory bowel diseases (IBD) (Crohn's disease and ulcerative colitis), and to differentiate IBD from irritable bowel syndrome (IBS) when used in conjunction with other diagnostic testing and the total clinical picture.

Literature Review

Randomized controlled clinical trial data are lacking regarding the clinical utility of fecal calprotectin testing to inform diagnosis, or predict relapse or response to treatment for IBD or any indication. Although patient numbers included in published studies are large, a number of study limitations have been identified by authors including uncontrolled and heterogeneous study design, and heterogeneous patient populations. Further, in some studies it is unknown whether FC samples were obtained before commencing treatment, which may be a major confounder in reports of diagnostic accuracy (Henderson, et al., 2013). In the study by Henderson (2013) the authors note "The assessment of methodological quality determined that there were deficiencies in all the studies evaluated, but especially with regard to important aspects, such as the use of a representative spectrum of patients, an acceptable reference standard (upper and lower endoscopy), and the poor reporting of current treatment modalities in use during FC sampling."

Inflammatory Bowel Disease (IBD): El-Matary et al. (2017) reported on a retrospective cohort study that examined the impact of fecal calprotectin (FCal) measurements on decision-making and clinical care of children with IBD. FCal, clinical activity indices, and blood markers were measured in 77 (115 fecal samples) children with diagnoses of IBD. Pearson correlation coefficient analysis was performed to examine association between FCal and other markers. Then decisions based on FCal measurements were prospectively documented and participants were evaluated three to six months later. FCal positively correlated with clinical activity indices ($r = 0.481$, $P < 0.05$) and erythrocyte sedimentation rate ($r = 0.40$, $P < 0.05$) and negatively correlated with hemoglobin ($r = -0.40$, $P < 0.05$). Sixty-four out of 74 (86%) positive FCal measurements ($\geq 250 \mu\text{g/g}$ of stools) resulted in treatment escalation with subsequent significant clinical improvement while in the FCal negative group, 34 out of 41 (83%) measurements resulted in no change in treatment and were associated with remission on follow-up. The study was limited by lack of randomization, retrospective design, and small sample size in particular for those for those who had colonoscopy.

Abej et al. (2016) reported on a prospective cohort study performed to determine the relationship between fecal calprotectin (FCAL) and imaging studies and other biochemical inflammatory markers and the impact of FCAL measurements on decision-making in IBD patient management in usual clinical practice. The study included 240 persons with IBD. The correlation between FCAL values and other markers for disease activity such as serum albumin (alb), hemoglobin (Hg), and C-reactive protein (CRP) and diagnostic imaging or colonoscopy were examined. FCAL $\geq 250 \text{ mcg/g}$ of stool was considered a positive result indicating active IBD. The results of 183 stool samples (76.3%) were returned. The return rate in the pediatric and adult cohorts was 91% ($n = 82$) and 67.3% ($n = 101$), respectively ($P < 0.0001$). Positive FCAL was associated with colonoscopy findings of active IBD ($P < 0.05$), low albumin ($P < 0.05$), anemia ($P < 0.01$), and elevated CRP ($P < 0.01$). There was no significant difference for FCAL results by outcomes on small bowel evaluation among the 21 persons with small bowel CD.

Most persons (87.5%) with normal FCAL and no change in therapy remained in remission during subsequent 3 months. Of 11 subjects with a positive FCAL who underwent imaging, only 6 had active disease on imaging; a positive FCAL was not significantly associated with radiologic evidence of active disease ($P = 0.31$). This study was limited by lack of controls, and the small number who underwent imaging and endoscopy.

Bar-Gil Shitrit et al. (2016) reported on a study that prospectively assessed the value of fecal calprotectin and lactoferrin in 68 patients with Crohn's disease (CD) to predict capsule endoscopy (CE) findings. Stool samples for calprotectin and lactoferrin and blood samples were collected for relevant parameters. Correlation between fecal markers and CE findings was assessed and receiver operating characteristic (ROC) curves were built to determine the predictive values of fecal markers for the diagnosis of CD. Fecal calprotectin data was available for all the patients and lactoferrin data for 38. CE findings compatible with CD were found in 23 (33%) patients and 45 (67%) were negative for CD. The average age of the CD group was 34 compared to 46 in the non-CD group ($p = .048$). Median calprotectin and lactoferrin in the CD group and in the control group were 169 mg/kg vs. 40 ($p = .004$) and 6.6 mg/kg versus 1 ($p = .051$), respectively. The area under the ROC curve was 0.767 for calprotectin and 0.70 for lactoferrin. A fecal calprotectin concentration of 95 mg/kg and fecal lactoferrin of 1.05 mg/kg had a sensitivity, specificity, positive predictive value and negative predictive value of 77 and 73%, 60 and 65%, 50 and 50%, and 84 and 84% in predicting CE findings compatible with CD. The study is limited by small number of participants and lack of controls.

Several meta-analyses of prospective and registry data have been performed to examine the predictive capacity of fecal calprotectin in individuals with IBD (e.g., Crohn's disease, ulcerative colitis). Reported results have been inconsistent with a wide variation in sensitivity and specificity of FC for included studies, ranging from 61-100% and 71-100%, respectively for diagnosis of IBD and other intestinal disorders. Sensitivity and specificity to predict relapse are 43-80% and 48-73%, respectively (Heida, et al., 2017; Henderson, et al., 2013; Kostakis, et al., 2012; Mao, et al., 2012; Jellema, et al., 2011; Laharie, et al., 2011; van Rheenen, et al., 2010; von Roon, et al., 2007).

In several studies (Hukkinen, et al., 2016; Henderson, et al., 2013; van Rheenen, et al., 2010), results regarding specificity of FC testing in children were significantly different compared with those for adults (96% and 68-97%, respectively). In addition, recent studies and meta-analysis have been published regarding the use of fecal calprotectin in management of IBD (Bressler, et al., 2015; Wright, et al., 2015; Kennedy, et al., 2015; Mosli, et al., 2015; Menees et al., 2015; Lin, et al., 2014; Sandborn, et al., 2016; Chey, et al., 2015). These studies examine the accuracy of the test, but do not indicate the clinical utility of fecal calprotectin in the management of IBD. The tests did not substantiate the use of this test in altering the management of the condition, or reducing or eliminating other testing for the condition.

Hayes published a directory report for fecal calprotectin (FC) assay for monitoring postoperative recurrence (PER) of Crohn Disease (CD) (2013, 2017). It was found that overall quality of the body of evidence pertaining to the use of FC testing systems for the evaluation of postoperative endoscopic recurrence (PER) in patients with CD was considered to be low with one study rated as good quality; five as fair quality; and, five as poor quality. The major individual study limitations included small sample sizes; study design; lack of blinding; no follow-up; unclear, extended, or varying lengths time between FC stool sample collection and colonoscopy; lack of correction for multiplicity in analysis; multiple endoscopic procedures per patient unaccounted for in the analysis; and nonuniform postoperative treatment. The study concluded that the available evidence indicates that FC testing generally has high negative predictive value (NPVs) and moderate sensitivity but low-to-moderate specificity and positive predictive value (PPVs) for the prediction of PER in patients with CD. With a high NPV, patients and clinicians can have a high assurance that a negative result on an FC test suggests that PER will not occur, thus potentially avoiding or delaying invasive endoscopic procedures. The study noted that however, NPVs and sensitivity values varied across some studies; thus, additional research is needed to define uniform and optimal cutoffs for FC testing to predict and monitor PER of CD. In addition, no direct evidence was available regarding the clinical utility of FC testing to change management or improve outcomes in patients with CD following ileocolic resection. Additional good-quality, blinded studies of sufficient size, design, and duration are required to evaluate the clinical utility of FC testing for monitoring PER of CD.

Hayes published a directory report for the use of fecal calprotectin (FC) assay for monitoring disease activity in Crohn disease (CD) (Hayes, 2013; 2017). The review found that in general, FC testing provides moderate-to-

high sensitivity, specificity, PPV, NPV, and diagnostic accuracy for the prediction of disease activity using endoscopic or clinical indices in patients with CD and that no studies directly addressed measures of clinical utility. The conclusions of the report included that:

- The available evidence suggests that FC testing is safe and may have promise for monitoring disease activity due to the moderate-to-high diagnostic sensitivity and accuracy of this test to predict disease activity in patients with CD. However, no direct evidence was available regarding the clinical utility (i.e., change in patient management or improved clinical outcomes) of FC testing for monitoring disease activity in patients with CD. In addition, the specificity, positive predictive value (PPVs), and negative predictive value (NPVs) varied across studies, and additional studies are required to define uniform cutoffs for FC testing to predict and monitor CD activity.
- Across 12 studies assessing FC testing for the prediction of endoscopic disease activity, sensitivity ranged from 70% to 94.1% and specificity ranged from 40% to 97%. PPV and NPV ranged from 48.5% to 98% and 40% to 96.6%, respectively. Four studies reported diagnostic accuracy, which ranged from 71% to 87%.
- In three studies, FC testing had 50% to 80% sensitivity and 74.4% to 88% specificity for monitoring changes in clinical disease activity. PPV and NPV ranged from 27.6% to 76% and 71% to 96.8%, respectively.
- In one study, FC testing had a moderately high specificity (82%), moderate NPV (75%), and very low sensitivity (37%) for detection of clinical loss of response (LOR) to infliximab in patients undergoing maintenance therapy.
- There do not appear to be any safety concerns with the use of FC testing to predict and monitor CD activity, although the potential risk for false-positive results could result in unnecessary endoscopic procedures.
- Additional good-quality, blinded studies of sufficient size, design, and duration in well characterized patient populations are required to evaluate the clinical utility of FC testing for monitoring disease activity in patients with CD.

Although several clinical trials reflect abnormal or elevated FC levels in individuals with inflammatory bowel disease compared with controls, the clinical utility of fecal calprotectin testing to impact management and improve overall health outcomes has not been demonstrated. Large randomized controlled trials are necessary to establish the role of FC testing when compared to available diagnostic tests.

Colorectal Cancer: Similar to IBD, RCT data are lacking in the published, peer-reviewed scientific literature to evaluate the clinical utility of FC testing for screening and diagnosis of colorectal cancer (CRC) in adults and children. Although levels of fecal calprotectin may be elevated in individuals with CRC compared with healthy control subjects, several meta-analyses of prospective and retrospective studies reflect inconsistent sensitivity and specificity with values of 36-75% and 64-84% respectively (von Roon, et al., 2007; Shitrit, et al., 2007). The role of FC testing as a means to diagnose CRC has not been established.

Other Intestinal Conditions: FC testing has also been proposed for other conditions such as irritable bowel syndrome, colonic polyposis, diverticular disease, and diarrhea (Tursi, et al., 2014; Licata, et al., 2012; Pezzilli, et al., 2008; Parsons, et al., 2014). Randomized controlled trial data are lacking in the published peer-reviewed scientific literature demonstrating the ability to impact care management or improve patient health outcomes with FC testing. Further, there is a lack of published literature reflecting that this is considered a standard of care option for these indications. At this time there is insufficient evidence to determine the role and clinical utility of such testing.

Professional Societies

American College of Gastroenterology (ACG): ACG published updated guidelines for management of Crohn's Disease in adults (Lichtenstein, et al., 2018). The guidelines include the following recommendation:

- **Diagnosis:** Fecal calprotectin is a helpful test that should be considered to help differentiate the presence of IBD from irritable bowel syndrome (IBS) (strong recommendation, moderate level of evidence).
- In patients who have symptoms of active Crohn's disease, stool testing should be performed to include fecal pathogens, Clostridium difficile testing, and may include studies that identify gut inflammation such

as a fecal calprotectin and may include studies that identify gut inflammation such as a fecal calprotectin. (summary statement , no level of evidence)

- Fecal calprotectin and fecal lactoferrin measurements may have an adjunctive role in monitoring disease activity. (summary statement , no level of evidence)

Level of evidence:

Moderate: (further research would be likely to have an impact on the confidence in the estimate of effect)

Recommendation grading:

Strength of a recommendation graded as "strong" when the desirable effects of an intervention clearly outweigh the undesirable effects.

Summary statements are descriptive and do not have associated evidence-based ratings.

American Gastroenterological Association (AGA): the AGA published a clinical care pathway for Crohn's disease. In the section for assessing inflammatory status, fecal calprotectin is listed along with other lab testing that includes CBC, CRP, CMP, and ESR. There is no evidence level included in the clinical care pathway.

Use Outside of the US

European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN)/North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN): In joint recommendations From these organizations fecal calprotectin (FC) and fecal leukocytes (FL) are described as markers of bowel inflammation that have been shown to correlate with clinical measures of disease activity in patients who have Crohn's disease. They note that they may help clinicians ascertain the nature and severity of disease, in particular if prior measurements are available for comparison. Although FC and FL have also been shown to have potential to predict relapse, there is insufficient evidence to recommend routine use of these markers for surveillance of Crohn's disease (Rufo et al., 2012).

National Institute for Health and Care Excellence (NICE): NICE published guidance for fecal calprotectin diagnostic tests for inflammatory diseases of the bowel (2013; 2017). Recommendations include:

- Fecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS) in adults with recent onset lower gastrointestinal symptoms for whom specialist assessment is being considered, if:
 - Cancer is not suspected, having considered the risk factors (for example, age) described in the NICE guideline on suspected cancer
 - Appropriate quality assurance processes and locally agreed care pathways are in place for the testing.
- Fecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of IBD or non-IBD (including IBS) in children with suspected IBD who have been referred for specialist assessment, if:
 - Appropriate quality assurance processes and locally agreed care pathways are in place for the testing.

World Gastroenterology Organisation (2015): The global guideline for irritable bowel syndrome (IBS), lists fecal inflammation marker (e.g., calprotectin) in the IBS Level I diagnostic cascade.

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Transanal Radiofrequency Therapy for Fecal Incontinence (e.g., SECCA Procedure) (CPT Code 46999)

Fecal incontinence is the inability to control the passage of gas, liquid and/or solid feces due to the loss of the coordinated function of the muscles and/or nerves of the rectum, anal canal, and pelvic floor. Treatment of minor incontinence (i.e., incontinence to flatus and occasional seepage of liquid stool) may be controlled by changes in diet and dietary habits, medication (e.g., bulking agents, antidiarrheal drugs), and bowel training (e.g., Kegel exercises, biofeedback). In the case of major incontinence (i.e., frequent loss of solid waste material) or incontinence unresponsive to conservative measures, surgical intervention may be indicated. In the event of an isolated sphincter defect, the standard surgical treatment is sphincteroplasty. Other surgical procedures include repair of rectocele or rectal prolapse and, in severe cases, fecal diversion (i.e., colostomy) (Kim, et al., 2009; Lefebure, et al., 2008; Rao, 2004; Wexner and Sands, 2003; Takahashi, et al., 2002).

Transanal radiofrequency therapy (e.g., Secca® procedure) is a proposed alternative therapy for the treatment of fecal incontinence for patients who have not responded to medical therapy and are not good surgical candidates or have failed surgical intervention. The Secca procedure is noninvasive, typically takes 30–45 minutes, and is performed in an outpatient setting under local anesthesia and sedation. It is also proposed that there are fewer complications following the Secca procedure compared to invasive surgical procedures.

Radiofrequency therapy is based on the theory that “collagen deposition and subsequent scarring may increase one’s ability to recognize and retain stool and permit improved continence” (Parisien and Corman, 2005). An anoscopic device uses four electrodes to deliver controlled radiofrequency energy to the sphincter muscles surrounding the anal canal. The energy creates precise, submucosal burn lesions, triggering collagen contraction. The lesions are subsequently resorbed, remodeling the tissue. The remodeling is proposed to improve barrier function of the anal sphincter (Efron, et al., 2003; Takahashi, et al., 2002).

U.S. Food and Drug Administration (FDA)

The Secca® System (Curon Medical Inc., Sunnyvale, CA) was approved by the FDA as a 510(k) Class II device for general use for electrosurgical coagulation and “for use specifically in the treatment of fecal incontinence in those patients with incontinence to solid or liquid stool at least once per week and who have failed more conservative treatment” (FDA, 2002).

Literature Review

The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review for treatments for fecal incontinence (Forte, et al., 2016). The review found only case series studies for SECCA procedure, no randomized controlled trials or observational studies were found. It was found that evidence was insufficient regarding this procedure.

There is insufficient evidence in the published peer-reviewed scientific literature to support the effectiveness of transanal radiofrequency therapy (e.g., Secca procedure) for the treatment of fecal incontinence. Studies are primarily in the form of prospective case series with small patient populations (n=8–50). With the exception of one, five-year study (Takahashi-Monroy, et al., 2008) follow-ups were short-term, ranging from 6–12 months. Various questionnaires (e.g., Fecal Incontinence Severity Index, Fecal Incontinence-related Quality of Life questionnaire, Vaizey scale) were utilized to measure quality of life (e.g., coping, depression, embarrassment) outcomes and results were inconsistent. Typically there were no significant improvements in physical component outcomes, such as anorectal manometry parameters, pudendal nerve motor latency, endoanal ultrasound results, and the thickness of internal anal sphincters. Some studies reported numerous complications while others reported no complications (Ruiz, et al., 2010; Kim, et al., 2009; Lefebure, et al., 2008; Takahashi-Monroy, et al., 2008; Felt-Bersma, et al., 2007; Efron, et al., 2003; Takahashi, et al., 2003). Studies comparing the use of transanal radiofrequency therapy to established medical and surgical treatment options are lacking.

Professional Societies/Organizations

American College of Gastroenterology (ACG): in the ACG clinical guideline for management of benign anorectal disorders (Wald, et al., 2014) for the treatment of fecal incontinence it is noted regarding the Secca procedure, that there is insufficient evidence to recommend radiofrequency ablation treatment to the anal sphincter (SECCA) at this time (no recommendation, insufficient evidence).

American Society of Colon and Rectal Surgeons: In their practice parameters for the treatment of fecal incontinence, the American Society of Colon and Rectal Surgeons (Tjandra, et al., 2007) discussed the medical (e.g., fiber intake, antidiarrheal agents, enemas, laxatives, suppositories, anal plug) and surgical (e.g., sphincter repair, injectable therapy, sacral nerve stimulation, dynamic graciloplasty, artificial bowel sphincter, stoma) treatment options for this condition. Based on studies by Takahashi et al. (2003) (n=10) and Efron et al. (2003) (n=50), the ASCRS stated that the Secca procedure may be useful for selected patients with moderate fecal incontinence.

Use Outside of the US

National Institute for Health and Care Excellence (NICE): In an interventional procedure guidance document, NICE (2011) (United Kingdom) stated that endoscopic radiofrequency therapy of the anal sphincter for the treatment of fecal incontinence raised no major safety concerns, but the procedure should only be carried out in units specializing in the assessment and treatment of fecal incontinence. NICE noted that further research is needed to clearly define the appropriate patient group for this procedure. The guidance was based on three case series with small patient populations (n=19–50).

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Endoscopic retrograde cholangiopancreatography (ERCP), with optical endomicroscopy (CPT code 0397T)

Optical microscopy, also known as confocal laser endomicroscopy (CLE), is an emerging endoscopic technology that permits high-resolution assessment of gastrointestinal mucosal histology at a cellular and sub-cellular level. CLE and endocytoscopy can be performed with probe-based systems that are passed through the working channel of an endoscope. A confocal miniprobe is a flexible probe-based system (Cellvizio, Mauna Kea Technologies, Paris, France) that is used as an alternative to a confocal laser endomicroscope. In probe-based confocal laser endomicroscopy (pCLE), both the laser scanning unit and light source are outside the body of the patient, which makes the confocal miniprobe a "passive" conduit. The miniprobes are very flexible and can be passed through the working channel of a standard endoscope. The indications for confocal laser endomicroscopy (CLE) are still being defined. In general, the technology is used to target biopsies of abnormal tissue and to avoid taking biopsies of normal tissue. A use of this technology that is being investigated is the differentiation of benign from malignant biliary strictures with probe-based CLE (Meining, [UpToDate], 2017).

U.S. Food and Drug Administration (FDA)

In 2012 the Cellvizio® 100 Series System and Cellvizio® System with Confocal Miniprobes received 510(k) premarket approval for the GastroFlex M™ series of Confocal Miniprobes which are intended to allow imaging of the internal microstructure of tissues in the upper gastrointestinal tract including biliary and pancreatic ducts, accessed by an endoscope or endoscopic accessories. The Cellvizio 100 Series is a confocal laser imaging system with a variety of fiber optic probes that is intended to allow confocal laser imaging of the internal microstructure of tissues in anatomical tracts, i.e. gastrointestinal or respiratory, accessed through an endoscope.

Literature Review

Fugazza et al. (2016) systematic review is to analyze the current literature on confocal laser endomicroscopy (CLE) and to evaluate the applicability and diagnostic yield of CLE in patients with gastrointestinal and pancreatobiliary diseases. The review included 102 prospective and retrospective clinical studies that evaluated the sensitivity, specificity, or accuracy of CLE. Regarding the use of CLE in biliary duct, it was found that the addition of CLE to histological examination results in a significant increase in diagnostic reliability. Currently, biliary strictures are staged using a combination of endoscopic ultrasound and advanced imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), or EUS, with endoscopic retrograde cholangiopancreatography (ERCP) typically used for tissue sampling, including biopsy and cytological brushing. The current sensitivity of each of these methods is quite low, ranging from 20% to 60%. The present meta-analysis demonstrated that combining CLE with ERCP yields high sensitivity (90%) in the assessment of biliary strictures. The authors conclude that although CLE has several promising applications, its use has been limited by low availability, high cost, and the necessity of specific operator training. The review noted that in order to implement CLE in routine clinical practice there is a need for further clinical trials with a particular focus on cost-effectiveness and medicoeconomic analyses, as well as standardized institutional training.

Meining et al. (2011) reported on a prospective observational multicenter study of 102 patients with indeterminate pancreaticobiliary strictures. Clinical information, ERCP findings, tissue sampling results, and pCLE videos were collected prospectively. A presumptive diagnosis was provided based on probe-based confocal laser endomicroscopy (pCLE) during the procedure before pathology results were available. Patients received at least 30 days of follow-up until definitive diagnosis of malignancy was established or one-year follow-up if index tissue sampling was benign. The main outcome measurements were diagnostic accuracy, sensitivity, specificity of ERCP-guided pCLE compared with ERCP with tissue acquisition. Eighty-nine patients were able to be evaluated with CLE, with 40 patients were proven to have cancer. CLE had a sensitivity of 98% and a specificity of 67% for diagnosing malignancy.

Professional Societies/Organizations

American Society for Gastrointestinal Endoscopy (ASGE): the ASGE published a technology evaluation status report on confocal laser endomicroscopy (ASGE, 2014). The report notes that on probe-based confocal

laser endomicroscopy (pCLE) allows in vivo real-time visualization of biliary strictures via a dedicated probe passed through a cholangioscope or catheter for ERCP. pCLE can provide real-time microscopic images of the biliary epithelium, thereby providing histological information that is not otherwise available during ERCP.

The report identified several issues pertaining to CLE that deserve further investigation:

- Further studies evaluating the applicability and practicality of CLE, especially in community settings are needed. Although it appears that the current studies of CLE seem promising, these have primarily been in academic centers and their generalizability in nonacademic practices is unknown.
- Additional studies evaluating the learning curve of CLE image interpretation, use of CLE devices, and additional time needed to perform the procedure are needed.
- The clinical efficacy of the technology and its cost-effectiveness compared with other available advanced imaging technologies needs further study.
- Improvements in CLE imaging and image interpretation are needed. Combining CLE imaging with newer molecular markers and the development of computer-based algorithms may be possible avenues for further research in this area.

The report concluded that CLE is an emerging technology that in the bile duct and within pancreatic cysts, it can provide surrogate real-time histological information that has previously been unavailable. The limitations of CLE include the high cost of the equipment and probes, the lack of proven efficacy compared with other widely available advanced imaging techniques, and the need for either intravenous or topical fluorescent contrast agents. The report notes that before the technology can be widely accepted, many further studies are needed to determine its clinical efficacy and evaluate its cost-effectiveness and its utilization in both academic and community settings.

Use Outside of the US

No relevant information

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Wireless Gastrointestinal Motility Monitoring System (SmartPill®) (CPT Code 91112)

The SmartPill Gastrointestinal (GI) Monitoring System® (The SmartPill Corporation, Buffalo, NY) has been proposed as an alternative testing method for the diagnosis of gastric conditions and intestinal motility disorders such as gastroparesis and chronic constipation. The system records pH and pressure measurements from the entire length of the gastrointestinal tract for use by physicians to aid in the evaluation of gastrointestinal motility diseases and conditions. Sensors on board an ingestible capsule measure pH and pressure as the capsule travels the length of the GI tract. Measurements are transmitted from the capsule within the GI tract via radiofrequency signal to a patient worn receiver and subsequently downloaded for analysis and review. Next, software performs data analyses providing the physician with a printable report containing regional gut transit times: gastric emptying or transit time (GET), small bowel transit time (SBTT), combined small and large bowel transit time (SLBTT), colonic transit time (CTT) and whole gut transit time (WGTT). The capsule is expelled naturally from the body.

U.S. Food and Drug Administration (FDA)

The SmartPill GI Monitoring System® was approved in 2006 by the U.S. by the Food and Drug Administration (FDA) under the 510(k) process. Indications for use state SmartPill is used in evaluating patients with suspected gastroparesis. In October 2009, the SmartPill was FDA-approved for the evaluation of colonic transit in patients with chronic constipation, to aid in differentiating slow and normal transit constipation. It is not indicated for use in children.

Literature Review

Hayes (2017) published a directory report for wireless capsule systems for diagnosis of gastroparesis and monitoring of gastrointestinal motility. The review included 13 studies of wireless capsule systems for detection of GI motility disorders that were reported in 14 publications with three cross-sectional comparative studies, seven prospective case-control studies, and three retrospective pretest/posttest studies. Wireless motility capsule (ten studies) or wireless capsule endoscopy (three studies) were compared to reference standards (i.e., gastric scintigraphy, small bowel barium transit, and radiopaque markers). The findings of the report note that although 13 studies were identified that compared wireless capsule systems with other methods for detection of GI motility disorders, these studies provide limited evidence concerning the accuracy of the wireless capsule systems and no reliable evidence that use of these systems improves patient outcomes.

The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review for wireless motility capsule (WMC) versus other diagnostic technologies for evaluating gastroparesis and constipation (Stein, et al., 2013). The review noted WMC appears to be accurate in detection of gastroparesis and slow-transit constipation and may provide increased diagnostic gain as compared with standard motility testing. While the strength of evidence (SOE) is low, the data were relatively consistent and suggested that this modality is no less sensitive than conventional testing. The review noted that the evidence is insufficient to determine whether use of WMC will improve outcomes of care.

Published studies in the peer-reviewed scientific literature are observational or retrospectively conducted with small populations. Although well-established motility testing methods exist, studies are not designed to provide comparison of the accuracy—including sensitivity, specificity, positive and negative predictive values—of the SmartPill to conventional tests as the reference standard in same symptomatic patient population. As a result no strong conclusions can be made regarding the clinical utility of this technology (Kuo, 2011; Rao, 2011a; Camilleri, 2010; Kloetzer, 2010; Sarosiek, 2010; Rao, 2009; Hasler, 2009; Kuo, 2008).

Professional Societies/Organizations

American College of Gastroenterology (ACG): The ACG Practice Guideline on Gastroparesis (Camilleri et al. 2013) notes that wireless capsule motility testing is an alternative approach for assessment of gastric emptying; however, further validation is required before it can be considered an alternate to scintigraphy for the diagnosis of gastroparesis. This is noted to be a 'Conditional recommendation, moderate level of evidence'.

American Gastroenterological Association (AGA): The AGA Medical Position Statement 'Diagnosis and Treatment of Gastroparesis' (Parkman, et al., 2004) states that GES of a radiolabeled solid meal is the best accepted method to test for delayed gastric emptying. The AGA Medical Position Statement Guidelines on Constipation (AGA, 2013) supports the use of special tests such as CTT, anorectal manometry, balloon-expulsion tests or defecography in refractory patients. Neither guideline addresses the use of SmartPill.

American and European Neurogastroenterology and Motility Societies: These organizations published guidelines with consensus recommendations on the indications and optimal methods for the use of transit measurements in clinical practice (Rao, et al., 2011b). The guidelines note that, "The WMC (wireless motility capsule) is a validated and standardized test. It is recommended for assessment of colonic transit time in subjects with constipation and those with suspected colonic disorders. It also provides measurements of regional and whole gut transit."

American Society of Colon and Rectal Surgeons (ASCRS): The ASCRS practice parameter for the evaluation and management of constipation notes that anorectal physiology and colon transit time investigations may help to identify the underlying etiology and improve the outcome in patients with refractory constipation. The practice position notes the measurement of colon transit time using radio-opaque markers in patients with suspected slow-transit constipation is inexpensive, simple, and safe (Ternent, et al., 2007).

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHN): The NASPGHN recommendations on evaluation and treatment of constipation in infants and children (2006) notes that an evaluation of colonic transit time with radiopaque markers may be helpful in children with a history of infrequent bowel movements who have no objective findings of constipation.

Use Outside of the US

National Institute for Health and Care Excellence (NICE): NICE published guidelines regarding assessing motility of the gastrointestinal tract using a wireless capsule. The guidelines note that:

- The evidence on assessing motility of the gastrointestinal tract using a wireless capsule raises no major safety concerns.
- There is evidence of efficacy in measuring gastrointestinal function but uncertainty about the clinical benefit of this, and about patient selection; therefore, this procedure should be used only with special arrangements for clinical governance, consent and audit or research.

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High Resolution Anoscopy (HRA) (CPT Codes 46601, 46607)

During an anoscopy the perianal area and distal rectum are examined. High resolution anoscopy has been proposed as a method to identify anal lesions in high-risk populations, and for use in screening for anal cytology. High resolution anoscopy uses an anoscope as well as a colonoscope or operating microscope for more detailed examination. After application of a 3% acetic acid solution and Lugol's iodine, the canal is inspected with the colonoscope. Areas with acetowhitening are examined for abnormal patterns and targeted biopsies are performed on areas suspicious for high-grade squamous intraepithelial lesion (HSIL). Correlation of biopsy results with anal cytology results has been variable (Lee, 2010).

Literature Review

Hayes published a directory report for high-resolution anoscopy (HRA) for the evaluation of anal lesions (2014; 2017). The report concluded that HRA exhibits high sensitivity and moderate specificity for detecting abnormal lesions in high-risk populations. The findings included that HRA is more sensitive than cytology in detecting potentially harmful lesions. There were few studies found that evaluated the capacity of HRA to detect high grade anal intraepithelial neoplasia and findings were too inconsistent to accurately make any determination regarding the validity of HRA for this use.

Randomized controlled clinical trial data are lacking to demonstrate improved health outcomes with the use of high-resolution anoscopy to detect anal cytology. However, there is support by a number of professional societies/organizations related to its use as diagnostic tool in individuals with a suspicious anal lesion, including high-grade suspicious intraepithelial lesion (HSIL) and anal dysplasia found in prior cytology/biopsy.

A case series by Chang (2002) reported on a prospective study of high resolution anoscopy directed surgery in 37 patients with high-grade squamous intraepithelial lesion. Twenty-nine patients tested positive for human

immunodeficiency virus (HIV), eight patients tested negative. Mean follow-up was 32.3 months for HIV-positive patients and 28.6 months in HIV-negative patients. No HIV-negative patient developed recurrent high-grade squamous intraepithelial lesions. Twenty-three of 29 HIV positive patients had persistent or recurrent high-grade squamous intraepithelial lesions (HSIL) ($p < .003$). Six patients underwent reoperation for HSIL; four recurred by six months. No patients developed incontinence, stenosis, postoperative infection, or significant bleeding after surgical treatment. Study limitations include small patient population and uncontrolled study design.

Professional Societies/Organizations

American Society of Colon and Rectal Surgeons (ACRS): The ACRS (Steele, et al., 2012) published practice parameters for anal squamous neoplasms. The guideline notes that targeted destruction guided by high resolution anoscopy is effective to identify, biopsy, and destroy low grade anal intraepithelial neoplasm [LGAIN]/high grade anal epithelial neoplasm [HGAIN] without the morbidity associated with wide local excision. The Guidelines also note that a comprehensive approach with cytology, high resolution anoscopy, targeted biopsies, and directed therapy has reported clearance of high grade anal intraepithelial neoplasm [HGAIN] in up to 80%, with progression to higher-grade disease and invasive cancer in less than 5%. therefore, expectant management with close follow-up may be considered in select cases depending on risk factors, comorbidities, and available resources. However, because of the high prevalence of concomitant cervical intraepithelial neoplasm, a referral to gynecology is recommended to complete the evaluation. Targeted destruction and close clinical long-term follow-up is appropriate therapy for LGAIN/HGAIN. (Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C)

Use Outside of the US

Ontario Health Technology Assessment Series (OHTAS): OHTAS (2007) notes that high resolution anoscopy rather than routine anoscopy-guided biopsy is considered to be the diagnostic standard.

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13C-Spirulina Gastric Emptying Breath Test (GEBT) (CPT code 91299)

Gastroparesis is a syndrome of objectively delayed gastric emptying in the absence of a mechanical obstruction and cardinal symptoms of nausea, vomiting, early satiety, bloating, and/or upper abdominal pain. In patients with suspected gastroparesis and no evidence of a mechanical obstruction on imaging or upper endoscopy, an assessment of gastric motility is necessary to establish the diagnosis of gastroparesis. Delayed gastric emptying on scintigraphy is required to establish the diagnosis of gastroparesis (Camilleri, [UpToDate], 2016). A more recent developed test, the 13C-Spirulina Gastric Emptying Breath Test (GEBT) (Cairn Diagnostics, Brentwood, TN) has been proposed as an alternative approach for the assessment of gastric emptying. While this test has the advantage of avoiding radiation associated with scintigraphy, further studies are needed before they can be routinely recommended for evaluation of delayed gastric emptying (Camilleri, [UpToDate], 2016).

A kit containing the specially labeled test meal and all components necessary to administer the test meal and collect breath samples is provided to the test administration site by Cairn Diagnostics. The collected breath samples are returned to Cairn's CLIA-certified clinical laboratory for analysis by gas isotope ratio mass spectrometry (GIRMS). The patient will eat a special test meal, and then additional breath samples are collected at specified times. Once the test meal is consumed, the carbon-13 in the Cairn GEBT test meal gives rise to carbon-13 labeled CO₂, or ¹³CO₂, which can be measured in the breath samples.

Literature Review

Szarka conducted a study to validate ¹³C-Spirulina platensis gastric emptying (GE) breath test (GEBT) with a standardized meal. The study included 38 healthy volunteers and 129 patients with clinically suspected delayed gastric emptying (GE) who underwent measurements at 45, 90, 120, 150, 180, and 240 minutes after a 238 kcal meal labeled test with 100 mg [¹³C]-S platensis and 0.5 mCi ^{99m}Tc. The authors established normal ranges for scintigraphy with the test meal, intra-individual and inter-individual coefficients of variation (COVs), and the ability of the GEBT breath percent dose excreted *1000 values to predict scintigraphic half-life and to categorize GE as delayed, normal, or accelerated. In healthy group, the 10th and 90th percentiles of half-life for scintigraphic GE with this meal were 52 and 86 minutes; intra-individual COVs for scintigraphy and the GEBT were, respectively, 31% and 27% at 45 minutes, 17% and 21% at 90 minutes, 13% and 16% at 120 minutes, 10% and 13% at 150 minutes, and 8% and 12% at 180 minutes. The inter-individual COVs at each time for the [¹³C] GEBT and scintigraphy were typically approximately 1%-4% lower than intra-individual COVs. Individual breath samples at 45, 150, and 180 minutes predicted GE category; at 80% specificity, 45- and 180-minute samples combined were 93% sensitive to identify accelerated GE, and 150- and 180-minute combined were 89% sensitive for delayed GE.

U.S. Food and Drug Administration (FDA)

¹³C-Spirulina Platensis Gastric Emptying Breath Test (Gastric Emptying Breath Test, [GEBT]) (Advanced Breath Diagnostics LLC, Brentwood TN) received premarket approval (PMA) April 2015. The Gastric Emptying Breath Test (GEBT), to be used with the GEBT test meal, is intended for use in the measurement of the rate of gastric emptying of solids and as an aid in the diagnosis of delayed gastric emptying (gastroparesis) in adult humans who are symptomatic for gastroparesis.

Contraindications include:

- Individuals with known hypersensitivity to Spirulina, egg, milk or wheat allergens should avoid the GEBT.
- Because the GEBT is an indirect multi-compartmental method of measuring gastric emptying, GEBT results may be inaccurate in individuals compromised with significant small bowel, pancreatic, liver and/or lung disease. Consequently GEBT should not be administered to patients with pulmonary dysfunction (e.g. COPD) and/or small bowel malabsorption.

Approval was based on the observation in a study of 115 patients who underwent simultaneous scintigraphy and spirulina ¹³C breath test. At 80 percent specificity, the ¹³C-spirulina breath test samples at 150 and 180 minutes had a combined sensitivity of 89 percent for delayed gastric emptying.

Professional Societies/Organizations

American College of Gastroenterology (ACG): ACG published clinical guidelines for management of gastroparesis. The recommendations include, "Alternative approaches for assessment of gastric emptying include wireless capsule motility testing and ¹³C breath testing using octanoate or spirulina incorporated into a solid meal; they require further validation before they can be considered as alternates to scintigraphy for the diagnosis of gastroparesis. (Conditional recommendation, moderate level of evidence)"

Use Outside of the US

No relevant information

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Coding/Billing Information Gastroenterology

Note: 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Anoscopy, High Resolution (HRA)

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

| CPT® Codes | Description |
|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <u>46601</u> | Anoscopy; diagnostic, with high-resolution magnification (HRA) (eg, colposcope, operating microscope) and chemical agent enhancement, including collection of specimen(s) by brushing or washing, when performed |
| <u>46607</u> | Anoscopy; with high-resolution magnification (HRA) (eg, colposcope, operating microscope) and chemical agent enhancement, with biopsy, single or multiple |

Additional Services Considered Experimental/Investigational/Unproven:

| CPT® *Codes | Description | Comment |
|------------------------|----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| <u>46999</u> | Unlisted procedure, anus | Considered Experimental/Investigational/Unproven when used to report transanal radiofrequency therapy for fecal Incontinence (e.g., SECCA procedure) |
| <u>83993</u> | Calprotectin, fecal | |
| <u>91112</u> | Gastrointestinal transit and pressure measurement, stomach through colon, wireless capsule, with interpretation and report | |
| <u>91299</u> | Unlisted diagnostic gastroenterology procedure | Considered Experimental/Investigational/Unproven when used to report 13C-Spirulina Gastric Emptying Breath Test |

| | | |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------|--------|
| | | (GEBT) |
| 0397T | Endoscopic retrograde cholangiopancreatography (ERCP), with optical endomicroscopy (List separately in addition to code for primary procedure) | |

*Current Procedural Terminology (CPT®) ©2017 American Medical Association: Chicago, IL.

Neurology

Quantitative Sensory Testing (QST) (CPT Codes 0106T, 0107T, 0108T, 0109T, 0110T; HCPCS Code G0255)

QST is a psychophysical test used to assess and quantify small and large-fiber sensory nerve function by the use of touch, thermal (i.e., hot and cold), pain, and/or vibratory sensations. QST, a noninvasive study, is proposed to be able to detect early, subtle changes in small and large sensory nerve fibers. It has been proposed as a complementary diagnostic and monitoring tool to be used with traditional testing (e.g., Semmes-Weinstein monofilaments, Rydel Seiffert graduated tuning fork) for the detection of sensory nerve abnormalities for conditions such as diabetic neuropathy, carpal tunnel syndrome, multiple sclerosis and vitamin B deficiencies. QST has also been proposed for multiple other indications including: identifying HIV-associated peripheral neuropathy, use before and after lumbar discectomy to analyze sensory nerve dysfunction in the lower-extremities, following greater saphenous vein stripping to evaluate postoperative sensory changes, and prior to and following spinal cord stimulation for patients with chronic neuropathic pain due to either failed back surgery syndrome or complex regional pain syndrome, evaluation of sexual dysfunction, peripheral nerve dysfunction, painful bladder syndrome, and radiculopathy.

Several limitations of QST have been documented including a potential for bias if the patient is cognitively impaired or desires an abnormal result. QST has no localizing value because it is reflective of the integrity of the entire sensory neuraxis from receptors to brain. Abnormal QST values may occur because of peripheral nerve or central nervous system dysfunction. The test may lack objectivity due to patient status (e.g., distraction, boredom, inattention, fatigue, drowsiness), which may be enhanced by the time it takes to complete the test (e.g., one to two hours). The inclusion of the patient's reaction time to a stimulus may distort the actual sensory threshold. Electrode size, site of stimulation, method and rate of change of the stimulation, method of obtaining patient's response, and variations in testing devices make reproducibility of the test results difficult. There is also a lack of standardization for testing procedures and reporting outcomes, therefore test execution may differ with different examiners. Due to these variables, it is proposed that quantitative sensory testing (QST) lacks the objectivity of conventional nerve conduction studies (Pavlovic, et al., 2010; Backonja, et al., 2009; Siemionow, et al., 2006; Chong, et al., 2004; Shy, et al., 2003).

The various testing methods and devices used for QST to determine sensory abnormalities include:

- Electrical current testing such as current perception threshold testing or sensory nerve conduction testing (sNCT) which assesses sensory function. Examples of these devices include the Medi-DX 7000 (Neuro-Diagnostic Associates, Laguna Beach, CA) and the Neurometer® CPT or s-NCT (Neurotron, Inc., Baltimore, MD).
- Pressure-specified sensory testing evaluates nerve function by detection of light, status, and moving touch. Devices include the NK Pressure-Specified Sensory Device™ (PSSD) (NK Biotechnical Engineering Co., Minneapolis, MN).
- Thermal testing is used to assess a distinction between predominantly C fiber and A-delta fiber activity by the application of cold and heat. Examples of thermal devices by Medoc Advanced Medical Systems LTD (Minneapolis, MN) include the Contact Heat-Evoked Potential Stimulator (CHEPS), GSA Genito, TSA-2001 Sensory Analyzer, and the TSA-2001 Sensory Analyzer.
- Vibration perception threshold testing, or vibratory testing, assesses large myelinated nerve fiber dysfunction and measures sensory thresholds. The VSA-3000 Vibratory Sensory Analyzer (Medoc Advanced Medical Systems, Eilat, Israel) and the Bio-thesiometer (Bio-Medical Instruments, Newbury, OH) are examples of these devices.

- Voltage-actuated sensory nerve conduction threshold (V-sNCT) testing is used to evaluate the sensitivity, specificity and predictive value of A-delta fibers to assess localized pain sources. These devices include the Neural-Scan (Neuro-Diagnostic Associates [NDA], Inc., Laguna Beach, CA).
- Pain-fiber nerve conduction testing (pf NCV), also referred to as pain fiber nerve testing, has been proposed as a method of evaluating the severity, location and distribution of pain associated with conditions such as radiculopathy and/or neuropathy. According to the American Association of Sensory Electrodiagnostic Medicine (AASEM, 2015), this type of nerve testing is noninvasive, employs the use of a device, such as the Axon II, Neural Scan, and is conducted using a voltage actuated stimulus (sensory nerve conduction) and a potentiometer to measure the amplitude of the action potential.

U.S. Food and Drug Administration (FDA): QST systems and devices are approved by the FDA 510(k) process and are classified either as a Class II device or an unclassified device.

Literature Review

Hayes published a technology directory report regarding quantitative sensory testing for the diagnosis of lower extremity peripheral neuropathy (Hayes 2014; 2017). The review included 29 prospective or retrospective cohort, cross-sectional, matched-group, or case-control studies that evaluated QST for detection of neuropathy or foot ulcer and/or amputation susceptibility. There were no studies identified that relied on QST to guide patient management. Findings of the report noted that all of the available studies of QST are of poor to very poor quality and the amount and consistency of evidence concerning QST for the diagnosis of neuropathy varies widely, depending on the type of QST and the indication for testing. Some evidence suggests that vibration QST has moderate to high accuracy for the diagnosis of neuropathy and that monofilament QST and vibration QST have moderate to high accuracy for the diagnosis of loss of protective sensation as reflected in susceptibility to foot ulcer and/or amputation as a consequence of neuropathy. It was noted that there is insufficient evidence to evaluate monofilament QST for the diagnosis of neuropathy or to evaluate thermal QST, ball bearing QST, 2-point discrimination QST, or tactile circumferential QST for the diagnosis of neuropathy or susceptibility to foot ulcer and/or amputation. The report concluded that the best available studies do not provide consistent evidence that quantitative sensory testing (QST) has high accuracy for the diagnosis of neuropathy or loss of protective sensation.

The clinical significance of QST has not been demonstrated in clinical trials (Atherton, et al., 2007; Soomekh, et al., 2006; Chong, et al., 2004; Shy, et al., 2003). Additionally, evidence in the published peer-reviewed scientific literature does not support the clinical utility of QST. Randomized controlled clinical trial data are scarce; studies are primarily in the form of nonrandomized comparative studies and case series with heterogeneous small patient populations, using a variety of different devices. QST has not been recommended as a stand alone test. Limitations of the studies include: weak study methodology; inability to verify data; lack of a control group; numbers of patients lost to follow-up; numbers of patients who did not complete all of the testing; lack of comparisons to conventional neurological tools; variations in testing parameters, equipment and protocol; and lack of randomization (Eisenberg, et al., 2006; England, et al., 2005/2008; Centers for Medicare and Medicaid Services, 2003).

Professional Societies/Organizations

American Academy of Orthopedic Surgeons (AAOS): In their guidelines on the diagnosis of carpal tunnel syndrome, AAOS (2007) noted that the physician should not routinely evaluate patients with suspected carpal tunnel syndrome with new technology such as pressure specified sensorimotor devices.

American Academy of Neurology (AAN): In a report on QST based on a review of 350 articles, the AAN (Shy, et al., 2003; reaffirmed 2008 and 2013) noted QST is a potentially useful tool for measuring sensory impairment for clinical and research studies. However, QST results should not be the sole criteria used to diagnose pathology". The AAN indicated that malingering and other nonorganic factors can affect the outcomes of the test results. They also noted that well-designed studies to compare the various types of QST devices and methodologies are indicated and should include patients with abnormalities detected solely by QST.

In a report on distal symmetric polyneuropathy (England, et al., 2005; reaffirmed 2008), the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation stated that QST was not recommended as a diagnostic tool because the sensitivities

and specificities varied widely among the studies, and the tests have inherent variability. QST is difficult to standardize, and reproducibility of results ranged from poor to excellent.

American Association of Electrodiagnostic Medicine (AAEM): The AAEM (Chong, et al., 2004) conducted a review of the literature on QST to assess the "methodology, reliability, reproducibility, limitations, and potential clinical applications" of these studies. The authors noted the following conclusions:

- QST is a reliable psychophysical test of large- and small-fiber sensory modalities.
- QST tests the integrity of the entire sensory axis from receptors to brain. Abnormalities do not localize dysfunction to the central or peripheral nervous system, or any particular location along the peripheral nervous system.
- QST is highly dependent on the full cooperation of the patient and may be falsely abnormal if the patient is biased toward an abnormal result or is cognitively impaired. No algorithm can reliably distinguish between psychogenic and organic abnormality.
- QST has been shown to be reasonably reproducible over a period of days or weeks in normal subjects. Since longitudinal QST studies of patients in drug trials are usually done over a period of several months to a few years, reproducibility studies on the placebo-controlled group should be included.
- The reproducibility of thermal thresholds may not be as good as that of vibration threshold.
- For individual patients, more studies are needed to determine the maximum allowable difference between two QSTs that can be attributed to experimental error.
- Different commercially available QST instruments have different specifications (thermode size, stimulus characteristics), testing protocols, algorithms, and normal values. Only QST instruments and their corresponding methodologies that have been shown to be reproducible should be used for research and patient care.
- The results of QST can only be interpreted properly if machine calibration and testing protocol are strictly followed.
- The literature does not allow a conclusion to be made regarding whether any QST instrument is better than another.

Use Outside of the US

European Federation Of Neurological Societies (EFNS): In their 2009 guidelines (Cruccu, 2009) on the assessment of neuropathic pain, EFNS stated that studies using qualitative sensory testing (QST) lack blinding, involve a broad spectrum of patients and controls, and only four of 50 new studies were prospective. The variability of methods, results, and patient populations (e.g., diabetic neuropathy, spinal cord injury, radiculopathy) prevent any conclusions from being drawn. The Society stated that qualitative sensory testing (QST) may be used to document the sensory profile, but the test "cannot be considered sufficient to separate differential diagnoses". "Quantitative sensory testing (QST) is helpful to quantify the effects of treatments on allodynia and hyperalgesia and may reveal a differential efficacy of treatments on different pain components". They "do not recommend the systematic measure of thermal stimuli except for pathophysiological research or treatment trials. A simple and sensitive tool to quantify pain induced by thermal stimuli in clinical practice is still lacking".

International Association for the Study of Pain (IASP®): In guidelines on neuropathic pain assessment (Haanpää, 2011), the Special Interest Group on Neuropathic Pain of the IASP (NeuPSIG) explains that QST is biased towards thermal, including nociceptive, testing, which means that it excludes assessment of large fiber function. According to NeuPSIG, more studies with complete somatosensory profiles are needed. Results of available studies have been inconsistent and conflicting. Since QST abnormalities are found in non-neuropathic pains, these tests cannot be taken as a conclusive demonstration of neuropathic pain. Further, NeuPSIG notes QST can be used in clinic along with bedside testing, but it cannot allow for estimation of the level of the lesion within the neuraxis. The relevance of QST to predict therapeutic outcome has yet to be established in prospective studies.

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Physiologic Recording of Tremor Using Accelerometer/Gyroscope (CPT Code 95999)

Accelerometers and gyroscopes are devices that may be used to objectively record and monitor motion and electrical activity of muscles to measure tremor in individuals with movement disorders. Recent studies have examined the clinical utility of these devices as an adjunct in diagnosis and measurement of functional ability and recovery in individuals with dyskenetic disorders.

U.S. Food and Drug Administration (FDA)

The FDA approved the Kinesia™ device (Cleveland Medical Service, Cleveland, OH) in April 2007 for the monitoring and recording of motion and electrical activity of muscle to quantify kinematics of movement disorders such as tremor for research and diagnostic purposes. The Tremorometer® (FlexAble Systems, Inc., Fountain Hills, AZ) received substantial equivalency FDA 510 (k) approval in January 2001. It is a system designed to improve the measurement and quantification of tremor in human patients regardless of the etiology.

Literature Review

Controlled clinical trial data are lacking to inform the utility of these devices, including the translation of measurements into meaningful outcomes. Cheung et al. (2011) performed a systematic literature review; reviewing 54 studies that used accelerometers to classify human movement and to appraise their potential to determine the level of activity of older persons in hospital settings. Outcome measures criteria were comparisons of derived classifications of postural movements and mobility against those made by using observations. A number of limitations to the study were noted including the number and type of accelerometers used for measurement, varied age of study participants (varied from teenager to >60 yrs). Most studies were limited by small sample size; 54% had 10 subjects or less. Methods for validating data were also varied. Of the accelerometer studies included in this review, only 17 were conducted on patients and the remaining were conducted on healthy subjects (n=37 studies). The authors note that the literature review indicates that only a limited number of studies have applied accelerometry to measure activities in patients, of which six studies were of older patients. These studies were limited by smaller sample sizes and use of multiple accelerometer devices attached to different body positions. The activity classification algorithms validated in small sample size studies with <6 patients are insufficient for clinical use. A suitable algorithm for application in geriatric rehabilitation settings needs to be generic and accurate in older patients with different levels of mobility impairment.

Gebruers et al. (2010) reported results of a systematic review assessing the clinical applicability of different accelerometry based measurement techniques in persons with stroke. Twenty-five articles were selected for inclusion; there were 4 randomized controlled trials (RCT). The authors noted that although the available evidence may suggest that accelerometers yield valid and reliable data about individuals with stroke, data are young, limiting the ability to draw consistent conclusions. Further research is necessary to investigate predictive value and responsiveness.

Use Outside of the US

No relevant information.

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Adrenal and Fetal Mesencephalic Transplantation for Parkinson Disease (HCPSC Code S2103)

There are scarce data in the published, peer-reviewed scientific literature regarding the current clinical use of adrenal-to-brain transplantation in humans for any indication. In a systematic review of the literature, the Agency for Healthcare Research and Quality ([AHRQ], 2003) noted that there is a lack of efficacy and substantial morbidity associated with the procedure for the treatment of Parkinson disease (PD). The AHRQ also concluded that adrenal medullary transplants are no longer performed to treat PD.

There is ongoing research in animal and human models relative to the use of fetal mesencephalic transplantation as a replacement source of dopamine-producing cells. In this procedure, fetal brain cells (i.e., neurons) that produce dopamine are implanted in the putamen or head of the caudate area of the brain, which is the area controlling movement. In theory, the transplanted neurons can replace the loss of normal dopamine-producing cells. These fetal cells may be human or xenogeneic (i.e., derived from a different species).

Clinical improvement was demonstrated in small numbers of individuals with PD undergoing transplantation of fetal tissue in several nonrandomized studies; however, results have not been replicated in double-blind sham-surgery controlled clinical trials (Olanow, 2003; Freed, 2001). Transplantation of fetal substantia nigra into the stratum has failed to show significant efficacy and has been associated with the side effect of transplant-induced off-medication dyskinesias. More recently, implanted dopamine neurons have been found to contain Lewy bodies, suggesting that they are dysfunctional and may have been affected by the PD pathological process (Olanow, 2009).

The data is scarce regarding the safety and effectiveness of xenogeneic fetal cells for any indication in humans. Schumacher et al. (2000) reported results of a case series study of 12 individuals with Parkinson disease who underwent unilateral implantation of embryonic porcine ventral mesencephalic tissue (Schumacher, 2000). In the medication-off state, total Unified Parkinson's Disease Rating Scale scores improved by 19% ($p=.01$). At the time of study publication there were no reported permanent complications. Limitations of the study include small size, uncontrolled study design, and short-term follow-up.

U.S. Food and Drug Administration (FDA)

The FDA Center for Biologics and Research regulates the transplantation of fetal/embryonic cells. Companies supplying cell and tissue-based products must register and list their products with the FDA.

Professional Societies/Organizations

American Academy of Neurology (AAN): The AAN in an evaluation of surgery for Parkinson's disease (Hallett, et al., 1999) recommended that adrenal-to-brain transplantation not be performed because of unacceptable risk to the patient. They further noted that the procedure was no longer being studied. Regarding fetal mesencephalic transplantation the AAN notes that, while the procedure is promising, it remains experimental due to lack of controlled clinical trials. The authors determined that there were small, nonrandomized case studies which noted functional improvement in some patients; however, unacceptably high levels of morbidity and mortality were associated with the procedure. Review of pathologic reports found that few transplanted cells survived long term, suggesting that benefit of the procedure would be of short duration.

The authors also reviewed the documented studies of fetal mesencephalic transplantation. Studies were small and nonrandomized. There was variation between the studies in the techniques utilized, the site of transplantation, the number of mesencephalons used, and the immune-suppressive regimen provided. In all of the studies some of the patients demonstrated improvement in motor function. The summary notes that while the

procedure is promising because it appears effective and has low morbidity and mortality, it is considered experimental because of the absence of controlled studies.

Use Outside of the US

No relevant information

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Whole Body and Select Head Hypothermia in the Neonate (CPT Code 99184)

Hypoxic ischemic encephalopathy is characterized by the need for resuscitation at birth, neurologic depression, seizures, and electroencephalographic abnormalities. No specific clinical intervention has been shown to alter outcome. Total body and selective head hypothermia (e.g., a reduction in brain temperature of two-five degrees) in the neonatal population have been proposed as a therapeutic intervention to reduce death as well as neurodevelopmental disabilities.

According to Gluckman et al. (2005) the neuroprotective effects of experimental cooling are dependent on both a sufficient duration of cooling and on the timing of initiation of cooling. Extended cooling for 24–72 hours, started as late as six hours after injury, has been associated with persistent protection.

Literature Review

Jacobs et al. (2013) reported on a Cochrane review regarding cooling for newborns with hypoxic ischemic encephalopathy to determine the effect of therapeutic hypothermia in encephalopathic asphyxiated newborn infants on mortality, long-term neurodevelopmental disability and clinically important side effects. The review included 11 randomized, controlled studies (=1505) with term and late preterm infants with moderate/severe encephalopathy and evidence of intrapartum asphyxia that compared the use of therapeutic hypothermia with standard care. The authors concluded that there is evidence from the trials included in the systematic review that therapeutic hypothermia is beneficial in term and late preterm newborns with hypoxic ischemic encephalopathy. They noted that cooling reduces mortality without increasing major disability in survivors. The benefits of cooling on survival and neurodevelopment outweigh the short-term adverse effects. The authors note that hypothermia should be instituted in term and late preterm infants with moderate-to-severe hypoxic ischemic encephalopathy if identified before six hours of age.

Shankaran et al (2005) reported results of a randomized controlled clinical trial of hypothermia in infants with a gestational age of at least 36 weeks who were admitted to the hospital at, or before six hours of age with either severe acidosis or peri-natal complications and resuscitation at birth. The infants had moderate or severe encephalopathy. Study participants were randomly assigned to standard care (control, n=106) or whole body cooling (i.e., esophageal temperature of 33.5 degrees Celsius for 72 hours, followed by slow re-warming, hypothermia group, n=102). Neurodevelopmental outcome was assessed at 18 to 22 months of age. The primary outcome was death or severe disability. Death or moderate or severe disability occurred in 44 % in the hypothermia group and 62 % of infants in the control group (p = 0.01). Twenty-four and 38 infants died in the hypothermia and control groups, respectively, (p = 0.08). The rate of cerebral palsy was 19% and 30% in the hypothermia and control groups, respectively (p = 0.20). Data suggest that whole-body hypothermia reduces the risk of death or disability in this patient population.

In a follow-up to this study Shankaran et al. (2012) reported long-term outcomes of evaluable study participants. Of the 208 trial participants, primary outcome data were available for 190. Of the 97 children in the hypothermia group and the 93 children in the control group, death or an intelligence quotient (IQ) score below 70 occurred in 46 and 58, respectively (p=0.06). In these same groups, death occurred in 27 and 41, respectively, in the hypothermia and control groups (p=0.04). Death or severe disability occurred in 38 and 53, respectively, in the hypothermia and control groups (p=0.03). The rate of the combined end point of death or an IQ score of less than 70 at six to seven years of age was lower among children undergoing whole-body hypothermia than among those undergoing usual care. Outcomes were not statistically significant. Data suggest that hypothermia results in lower death rates; the rates of severe disability among survivors did not increase in the group undergoing hypothermia.

Azzopardi et al. (2009) performed a randomized controlled study of infants who were less than six hours of age and had a gestational age of at least 36 weeks and peri-natal encephalopathy. The study compared outcomes for infants receiving intensive care plus whole body hypothermia 33.5 degrees Celsius for 72 hours (n=163) with intensive care alone (n=162). The primary outcome was death or severe disability at 18 months of age. In the group undergoing hypothermia 42 infants died; 32 infants survived but had severe neurodevelopmental disability. In the intensive care treatment arm 44 infants died and 42 had severe disability (p = 0.17). Infants in the cooled group had an increased survival without neurological abnormality (p = 0.003). Among survivors, cooling resulted in reduced risks of cerebral palsy (p = 0.03) and improved scores on the Mental Developmental and Psychomotor Developmental Indexes of the Bayley Scales of Infant Development II (p = 0.03 for each) and the Gross Motor Function Classification System (p = 0.01). Data suggest that moderate hypothermia for 72 hours did not significantly reduce the combined rate of death or severe disability but resulted in improved neurological outcomes in survivors who received hypothermia.

In a multi-center randomized controlled trial Zhou et al (2010) examined the safety and the effectiveness of selective head cooling (SHC) with mild systemic hypothermia (i.e., nasopharyngeal temperature of 34+/- 0.2 C and rectal temperature of 34.5-35.0 Celsius for 72 hours) in infants with hypoxic ischemic encephalopathy (HIE). Infants were randomly assigned to the SHC or the control group. SHC was initiated within six hours after birth for infants in the hypothermia group. Rectal temperature was maintained at 36.0 to 37.5 degrees Celsius in the control group. Neurodevelopmental outcome was assessed at 18 months of age. The primary outcome was a combined end point of death and severe disability. The combined outcome of death and severe disability, mortality rate, and severe disability rates were significant (p = 0.01; p = 0.16; and p = 0.01) for the SHC and control groups, respectively. Data suggest that SHC with mild systemic hypothermia may significantly decrease the combined outcome of severe disability and death, as well as severe disability.

Professional Societies/Organizations

American Heart Association (AHA): In a special report, the AHA published Neonatal Resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Kattwinkel, et al., 2010). Regarding therapeutic induced hypothermia the AHA recommendation notes that infants born at ≥ 36 weeks gestation with evolving moderate to severe hypoxic ischemic encephalopathy should be offered therapeutic hypothermia. The treatment should be implemented according to the studied protocols, which currently include commencement within six hours following birth, continuation for 72 hours, and slow rewarming over at least four hours. Further, therapeutic hypothermia should be administered under clearly

defined protocols similar to those used in published clinical trials and in facilities with the capabilities for multidisciplinary care and longitudinal follow-up.

Use Outside of the US

No relevant information

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Percutaneous or Open Implantation of Electrode Array (CPT codes 64999)

Percutaneous or open implantation of a neurostimulator electrode array is a technique being investigated for treatment of chronic pain where stimulation is delivered by a pulse generator and an electrode that is placed subcutaneously at the site of maximum pain rather than at the site of the nerve. This technique also referred to as subcutaneous target stimulation (STS) or peripheral nerve field stimulation (PNFS) involves a temporary trial period in which an electrode is placed subcutaneously by open or percutaneous approach, is secured in place with suture, and is then attached to a generator for approximately two to 14 days. A trial is considered successful if there is at least 50% pain reduction. Following a successful temporary trial the device is implanted

U.S. Food and Drug Administration (FDA): FDA approval for specific PNFS devices was not found on the FDA site. However, PNFS can be carried out using leads and electrodes that are primarily designed for spinal cord stimulation and may be considered an off-label use of these devices.

Literature Review

Randomized controlled clinical trial data, and meta-analyses are lacking in the published, peer-reviewed scientific literature and there is insufficient evidence to determine safety and effectiveness of this therapy. Published peer-reviewed clinical trial data is primarily limited to case series and retrospective reviews.

Use outside of the US

The National Institute for Health and Care Excellence (UK, [NICE], 2013) published guidance regarding peripheral field nerve stimulation for chronic low back pain. NICE recommendations note that evidence on efficacy is very limited, in both quality and quantity. Likewise, evidence on safety is also limited and there is a risk of complications from any implanted device. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

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External Heart Rate and 3-Axis Accelerometer Monitoring to Diagnose Nocturnal Epilepsy (CPT Codes 0381T, 0382T, 0383T, 0384T, 0385T, 0386T)

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures (Abou-Khalil, 2012). Standard evaluation and diagnosis of seizures and epilepsy includes an in-depth clinical history; an electroencephalogram and other brain imaging may be used to supplement the history, help classify the type of seizure and determine underlying pathology. A number of epileptic seizure syndromes exist including several which are characterized by the occurrence of seizures at night, while the individual is sleeping and unattended. Nocturnal seizures often occur in children. Use of external heart rate and 3-axis accelerometer monitoring has been proposed as a method to detect/diagnose nocturnal epilepsy. Three-axial accelerometer measures the movement (acceleration) in three orthogonal directions fixed to a sensor by way of soft bands generally affixed to the wrists and/or ankles.

Literature Review

Published, peer-reviewed data are limited regarding the effectiveness of accelerometer monitoring to diagnose epilepsy, including nocturnal epilepsy (Beniczky, 2013; Van de Vel, 2013). Studies are limited by uncontrolled design, small participant numbers and short-term follow-up.

Beniczky et al. (2013) reported outcomes of a prospective study designed to assess the clinical reliability of a wrist-worn, wireless accelerometer sensor for detecting generalized tonic-clonic seizures in 73 consecutive patients. The wireless wrist accelerometer correctly detected 35 seizures (89.7%). The mean sensitivity per patient (with seizure) was 91%. Twenty-eight seizures occurred during sleep and eleven seizures occurred when the patient was awake. The device had a similar accuracy for detecting nocturnal and daytime seizures. One hundred forty-nine seizures other than generalized tonic-clonic seizures were recorded (simple partial, 37; complex partial/psychomotor, 31; focal tonic, 6; hypermotor, 6; absence, 1; myoclonus, 60; psychogenic nonepileptic seizure, 8). Study limitations include uncontrolled design, small study numbers and short-term follow-up.

Use Outside of the US

No relevant information

References

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Coding/Billing Information Neurology

Note: 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Whole Body or Selective Head Therapeutic Hypothermia

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

| CPT® Codes | Description |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 99184 | Initiation of selective head or total body hypothermia in the critically ill neonate, includes appropriate patient selection by review of clinical, imaging and laboratory data, confirmation of esophageal temperature probe location, evaluation of amplitude EEG, supervision of controlled hypothermia, and assessment of patient tolerance of cooling |

Neurology Services Considered Experimental/Investigational/Unproven:

| CPT® Codes | Description | Comment |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <u>64999</u> | Unlisted procedure, nervous system | Considered Experimental/Investigational/Unproven when used to report implantation of trial or permanent electrode arrays or pulse generators for peripheral subcutaneous field stimulation |
| <u>95999</u> | Unlisted neurological or neuromuscular diagnostic procedure | Considered Experimental/Investigational/Unproven when used to report tremor measurement with accelerometer(s) and/or gyroscope(s) |
| <u>0106T</u> | Quantitative sensory testing (QST), testing and interpretation per extremity; using touch pressure stimuli to assess large diameter sensation | |
| <u>0107T</u> | Quantitative sensory testing (QST), testing and interpretation per extremity; using vibration stimuli to assess large diameter fiber sensation | |
| <u>0108T</u> | Quantitative sensory testing (QST), testing and interpretation per extremity; using cooling stimuli to assess small nerve fiber sensation and hyperalgesia | |
| <u>0109T</u> | Quantitative sensory testing (QST), testing and interpretation per extremity; using heat-pain stimuli to assess small nerve fiber sensation and hyperalgesia | |
| <u>0110T</u> | Quantitative sensory testing (QST), testing and interpretation per extremity; using other stimuli to assess sensation | |
| <u>0381T</u> | External heart rate and 3-axis accelerometer data recording up to 14 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional | |
| <u>0382T</u> | External heart rate and 3-axis accelerometer data recording up to 14 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only | |
| <u>0383T</u> | External heart rate and 3-axis accelerometer data recording from 15 to 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional | |
| <u>0384T</u> | External heart rate and 3-axis accelerometer data recording from 15 to 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only | |
| <u>0385T</u> | External heart rate and 3-axis accelerometer data recording | |

| | | |
|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| | more than 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional | |
| 0386T | External heart rate and 3-axis accelerometer data recording more than 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only | |

| HCP Codes | Description |
|-----------|----------------------------------------------------------------------------------------|
| G0255 | Current perception threshold/sensory nerve conduction test, (sNCT) per limb, any nerve |
| S2103 | Adrenal tissue transplant to brain |

*Current Procedural Terminology (CPT®) ©2017 American Medical Association: Chicago, IL.

Obstetrics/Gynecology

Laparoscopic Radiofrequency Ablation (RFA) of Uterine Fibroids (CPT codes 58674)

Laparoscopic RFA has been proposed for the treatment of uterine fibroids of all sizes. In this minimally invasive procedure a laparoscopic ultrasound probe is used to determine the location and size of fibroids. An electrode array delivers alternating radiofrequency energy to drive a current through the tissue to be ablated, causing controlled, local heating, resulting in targeted tissue destruction.

U.S. Food and Drug Administration (FDA): The Acessa System (Halt Medical, Inc., Brentwood, CA) was given 510(k) approval in November 2012. According to the approval summary this system is indicated for use in percutaneous, laparoscopic coagulation and ablation of soft tissue, including treatment of symptomatic uterine fibroids under laparoscopic ultrasound guidance. The FDA specifically notes the Acessa System must be used under laparoscopic ultrasound guidance. Laparoscopic ultrasound equipment is not included with the Acessa System.

Literature Review

Peer-reviewed published clinical trial data are limited to a single small randomized controlled trial of 51 women with 26 subjects in the RFA treatment arm (Brucker, 2014; Hahn, et al., 2015; Kramer, et al., 2016) and several nonrandomized, uncontrolled prospective studies, also with small participant numbers. Chudnoff et al. (2013), Guido et al. (2013) and Berman et al. (2014) reported 12-, 24- and 36-month follow-up of the same nonrandomized prospective interventional trial involving 135 women with symptomatic uterine fibroids. These studies are limited by uncontrolled, nonrandomized study design, small size and lack of comparison to other treatment methods. Several randomized controlled studies are ongoing.

Brucker et al. (2014) reported outcomes of a randomized, prospective single-center international clinical trial involving 51 women comparing radiofrequency volumetric thermal ablation (RFVTA) (n=26) and laparoscopic myomectomy (LM) (n=25) for symptomatic uterine fibroids. Primary outcomes were the mean hospital discharge times and perioperative outcomes. The predominant symptom reported by the patients in both groups was heavy menstrual bleeding followed by urinary frequency, pelvic discomfort and pain, backache, localized pain, dysmenorrhea, urinary retention, increased abdominal girth, dyspareunia, uterine pain, and sleep disturbance. There were no significant differences based on Fisher exact test between the two groups with regard to any of these symptoms, although the authors note this could be because of the relatively small number of patients in each group. Surgeons were blinded to the treatment until all fibroids were mapped by laparoscopic ultrasound. The mean hospitalization times were 10.0± 5.5 hours for the RFVTA group and 29.9 ± 14.2 hours for the LM group (p=.16). Intraoperative blood loss was 16 mL for the RFVTA procedures and 51 mL for the LM procedures. The percentage of fibroids imaged by laparoscopic ultrasound that were treated/excised was 98.6% for RFVTA and 80.3% for LM. Two complications were reported: vertigo (n=1; RFVTA) and port site hematoma (n=1; LM).

The mean time between arrival in post-anesthesia recovery and discharge from the hospital was 8.2 hours for the RFVTA group and 28.0 hours for the LM group ($p < 0.001$). Mean hospitalization time was 10.0 hours and 29.9 hours for the RFVTA and LM groups, respectively, $p < 0.001$. The authors note that short-term follow-up is a limitation to the study and plan five-year follow-up for pregnancy outcomes, symptom improvement, and overall treatment satisfaction as evaluated on the basis of participants' responses to validated questionnaires. The study is limited by small study participant numbers.

Hahn et al. (2015) published one year results of the above study (Brucker, et al., 2014) with objective to analyze, compare and describe the study's three, six and twelve month outcomes in terms of pain medication use, recovery from surgery, and subjects' subjective responses to validated questionnaires. The results included: post-surgery, ablation and myomectomy subjects took pain medications for 4 days (range: 1–46) and 7 days (range: 1–83 days) respectively ($p = 0.60$); ablation and myomectomy patients missed 10.0 workdays (range: 2–86 days) and 17.0 workdays (range: 7–30 days) ($p = 0.28$); resumed normal activities in 20.5 days (range: 5–103 days) versus 28.0 days (range: 10–42 days) ($p = 0.86$) respectively. The mean symptom severity scores decreased (improved) by -7.8 for the ablation subjects and by -17.9 for the myomectomy subjects ($p = 0.16$). Health-related quality of life improved (increased) by 7.5 and 13.1, respectively, for the two groups ($p = 0.46$). Two myomectomy subjects had pregnancies that ended in a Cesarean delivery and a vaginal delivery of healthy infants. Two pregnancies in the RFVTA group ended in full-term vaginal deliveries of healthy infants. The authors concluded that early postoperative recovery and twelve-month results indicate similar efficacy, quality of life, and safety for both treatment groups. The subjects will be continued to be followed for five years.

Kramer et al. (2016) reported on 24 month data from the above study (Brucker, et al., 2014). The outcomes included this analysis were patients' responses to validated questionnaires and long-term safety. The study included 51 patients with 21 and 22 patients in the RFVTA and laparoscopic myomectomy groups, respectively that completed 24 months of follow-up. There was improvement reported in the severity of symptoms from baseline by participants in both the RFVTA ($P < 0.001$) and laparoscopic myomectomy groups ($P = 0.001$). The study observed a significant improvement in health-related quality of life in the laparoscopic myomectomy group ($P = 0.040$); and a non-significant improvement was noted in the RFVTA group ($P = 0.083$). A trocar-site hematoma occurred in one patient in the laparoscopic myomectomy group. There were further surgical interventions recorded in three patients in the RFVTA group but it was noted that these were unrelated to fibroid symptoms.

Hayes evaluated the safety and efficacy the Acessa System for treatment of uterine fibroids (Hayes, 2014; 2017). They noted that the all of the included studies found significant benefits of treatment of uterine fibroids with the Acessa System, and longer-term studies demonstrated the durability of the treatment effect. Treatment reduced pain, heavy bleeding, and other symptoms, and improved quality of life. They found that the overall quality of the evidence is low. Five of the six studies lacked a control group, and the single, randomized, clinical trial only reported on perioperative outcomes with no long-term follow-up. Many of the study endpoints were subjective. Additional studies evaluating larger populations and that include control groups and head-to-head comparisons with other treatments for uterine fibroids are warranted to determine the optimal clinical role of this technology.

Chudnoff et al. (2013) reported one year results of a prospective, multicenter, interventional clinical trial (i.e., HALT trial) with primary outcome measures of change from baseline to 12 months and ongoing qualitative follow-up of women for three years in a cohort of 135 premenopausal symptomatic women with uterine myomas, uteri 14 weeks of gestation-sized or less with no single myoma exceeding 7 cm, and objectively confirmed heavy menstrual bleeding. Primary intervention was outpatient laparoscopic ultrasound-guided radiofrequency volumetric thermal ablation using the Acessa system (Halt Medical, Brentwood, CA). Bleeding outcomes and validated quality-of-life and patient satisfaction scales and objective measurements of uterine and myoma volume were conducted at 3, 6, and 12 months. Mean alkaline hematin and associated menstrual blood loss decreased from baseline levels by 31.8%, 40.7%, and 38.3%, respectively, at three-, six-, and 12-month intervals ($p < .001$ for all). Symptom severity and health-related quality of life improved ($p < .001$). There was one serious adverse event (0.7%) requiring readmission 5 weeks post-procedure and one surgical reintervention for persistent bleeding. Ninety-four percent of the women reported satisfaction with the treatment ($p < .001$). The study was limited by uncontrolled design, short-term follow-up and a lack of comparison to other treatment methods.

In a follow-up to the study by Chudnoff et al. (2013), Guido et al. (2013) reported two-year outcomes of 124 subjects who participated in the HALT trial, of whom 112 were evaluable. Outcome measures included: subject responses to validated questionnaires, treatment-emergent adverse events, and surgical re-intervention for fibroids at 24 months post-procedure. Significant changes from baseline were noted in symptom severity ($p < .001$) and health-related quality of life scores ($p < .001$). There was a significant improvement in the mean health state score between baseline and 3 months after treatment ($p < .001$). Measurements at subsequent intervals showed no continued improvement. Six patients underwent surgical reintervention for fibroid-related bleeding between 12 and 24 months. The authors also reported on one patient who had an episode of bleeding post Cesarean section requiring receipt of six units of blood, which the study authors noted as possibly related to the RFA procedure. Limitations to the study include uncontrolled design, lack of comparator, short-term follow-up and small total patient numbers.

In a thirty-six month follow-up study, Berman et al. (2014) reported subject responses to validated questionnaires and surgical repeat intervention to treat myomas outcomes for a cohort of 104 evaluable patients (104/135) who participated in the HALT trial. Change in mean symptom severity ($p < .001$) and Health-Related Quality of Life questionnaire scores ($p < .001$) were improved from the baseline. Patient-reported Uterine Fibroid Symptom and Health-Related Quality of Life questionnaire subscores demonstrated statistically significant improvement from baseline to 36 months ($p < .001$) in all categories (i.e., Concern, Activities, Energy/Mood, Control, Self-consciousness, and Sexual Function). The cumulative repeat intervention rate was of 11% at 36 months. Although results are promising, study limitations include uncontrolled, nonrandomized design, lack of comparison to other treatment methods, and small study participant numbers.

Robles et al. (2013) assessed outcomes of a prospective study assessing the laparoscopic radiofrequency volumetric thermal ablation (RFVTA) system among 114 screened women with symptomatic myomas. Thirty-five women completed the 12-month follow-up period. Uterine fibroid symptom and health-related quality-of-life (UFS-QOL) questionnaires were completed at zero, three-, six-, and 12-months. There was a significant reduction in average symptom severity score over the study period ($p < 0.001$), and reductions in symptom severity scores from baseline to each of the follow-up visits, and from the 3-month visit to the 12-month follow-up visit were significant ($p < 0.001$). There was a significant increase in average health-related quality of life (HRQL) scores from baseline to 12 months ($p < 0.001$) and in the HRQL scores from baseline to each of the follow-up visits ($p < 0.001$). After discharge, none of the participants was admitted to hospital for procedure-related complications. Within the study period, none of the participants required hysterectomy or any myoma treatment after RFVTA. No transfusions were required. Nine adverse events among eight women were reported as definitely not device- or procedure-related. Study limitations which limit the ability to routine clinical practice include lack of randomization and control, small study population, short-term follow-up of 12 months and lack of comparison to other treatment methods.

Thirty-one women with symptomatic uterine fibroids underwent outpatient laparoscopic, ultrasound-guided, radiofrequency volumetric thermal ablation using the Halt 2000 System. Postoperative follow-up occurred at three, six, and 12 months. The primary outcome measures were patient safety, frequency of adverse events, repeat intervention rate, symptom severity and health-related quality-of-life scores from the validated Uterine Fibroid Symptom and Quality-of-Life Questionnaire. Secondary outcome measures were uterine volume changes over time. Mean symptom severity scores improved significantly compared with baseline at three, six, and 12 months. Mean health-related quality-of-life scores reached statistical significance over time. Mean uterine volume decreased at three six, and 12 months. There were no procedure-related repeat hospitalizations, repeat treatments or procedures related to fibroid symptoms following treatment. The study is limited by lack of randomization and control, short-term follow-up, small sample size and lack of comparison to other treatment methods. Larger multicenter studies are needed to confirm these results (Garza, 2011).

Professional Societies/Organizations

American Association of Gynecological Laparoscopists (AAGL):

The AAGL published practice guidelines for the diagnosis and management of submucous leiomyomas (2012) which note with currently available evidence, embolic and ablative therapies, including leiomyoma ablation with radiofrequency electricity are not appropriate for women with submucous myomas who have current infertility or who wish to conceive in the future. The guidelines do not address embolic or ablative therapies related to submucous myomas for individuals without infertility or who do not desire future conception.

Use Outside of the US

Society of Obstetricians and Gynaecologists of Canada (SOGC): the SOGC published evidenced-based guidelines for the management of uterine leiomyomas (Vilos, et al., 2015). The recommendations note that, "Of the conservative interventional treatments currently available, uterine artery embolization has the longest track record and has been shown to be effective in properly selected patients: (II-3) Newer focused energy delivery methods are promising but lack long-term data. (III)". The newer methods included in this statement includes radiofrequency ablation of uterine fibroids.

Quality of evidence assessment:

III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

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Coding/Billing Information Obstetrics/Gynecology

Note: 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Obstetrics/Gynecology Services Considered Experimental/Investigational/Unproven:

| CPT® Codes | Description |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| <u>58674</u> | Laparoscopy, surgical, ablation of uterine fibroid(s) including intraoperative ultrasound guidance and monitoring, radiofrequency |

*Current Procedural Terminology (CPT®) ©2017 American Medical Association: Chicago, IL.

Ophthalmology

Suprachoroidal Delivery of Pharmacological Agent (CPT Code 67299) Suprachoroidal Injection of a Pharmacologic Agent (does not include supply of medication (CPT code 0465T)

The leading causes of blindness include those affecting the back of the eye: age-related macular degeneration, diabetic retinopathy, and uveitis. Although treatments are available, delivering drugs to the posterior regions of the eye is challenging because of architecture as well as natural barriers (Patel, 2011). Drug delivery techniques include intravitreal injections, periocular injections and intravitreal implants. Suprachoroidal drug delivery has been proposed as an alternative method to access the suprachoroid space (SCS). There have been several techniques described for injections into the SCS (Moisseiev, et al., 2016). The injection can be done using standard small-gauge needles, but this is a delicate procedure with a risk of penetration into the choroid or the vitreous cavity. Surgical cannulation may be used for drug delivery to the posterior pole, however, this is a complicated procedure and cannot be performed in-office. SCS drug delivery using microneedles is also being investigated. The micro-needles are small-gauge needles (30–33 G) and 0.7–1.0 mm in length that are only long enough to penetrate the sclera and reach the SCS. These microneedles have been demonstrated to be safe and effective in several animal studies. SCS™ microinjector (Clearside Biomedical Inc. Alpharetta, GA), is a microneedle being developed for SCS injection in humans. The device is currently undergoing two Phase 2 clinical trials with its proprietary formulation of triamcinolone acetonide (CLSTA) for the treatment of macular edema associated with noninfectious uveitis and along with aflibercept for the treatment of macular edema associated with RVO.

U.S. Food and Drug Administration (FDA)

The iScience Surgical Ophthalmic Microcannula (iScience Surgical Corporation, Redwood City, CA) is a flexible microcannula designed to allow atraumatic cannulation of spaces in the eye such as the anterior chamber and posterior segment (FDA, 2004). It received 510(k) approval on June 22, 2004 for the following indications: fluid infusion and aspiration, as well as illumination, during surgery.

SCS™ microinjector (Clearside Biomedical Inc. Alpharetta, GA) has not yet received FDA approval.

Literature Review

Randomized control trial data are lacking to demonstrate the safety and effectiveness of suprachoroidal delivery of pharmacological agents for any indication, including injection of pharmacologic agents. Studies are limited by uncontrolled design and small populations.

Professional Societies/Organizations

Guidelines of the American Academy of Ophthalmologists do not include suprachoroid delivery as a method for delivering drugs to the posterior regions of the eye.

Use Outside of the US

No relevant information.

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Conjunctival Incision with Posterior Extrasccleral Placement of a Pharmacological Agent (CPT Code 68399)

Neovascular age-related macular degeneration (AMD) is associated with a rapid loss of vision due to an abnormal growth of blood vessels in the macula of the eye, leakage, and scarring (Geltzer, 2007). Treatment options for this disease are limited and there are a variety of therapies currently being investigated for neovascular AMD. Surgical implantation of steroids with antiangiogenic and anti-inflammatory properties has been proposed as a practical method of administering these agents into the eye (Geltzer, 2007). Extrasccleral placement of steroids involves an incision into the orbit posterior to the limbus, through the conjunctiva. A cannula is inserted outside the sclera until the tip is near the macula, and the drug is administered. Advantages to this procedure may include a reduced risk for retinal detachment and endophthalmitis (Geltzer, 2007).

Literature Review

Randomized controlled trial (RCT) data are scarce regarding the safety and effectiveness of conjunctival incision with posterior juxtascleral placement of pharmacological agents.

Geltzer et al. (2013) reported on a Cochrane review which analyzed outcomes of three RCTs involving the administration of triamcinolone acetonide versus placebo, anecortave acetate versus placebo, and anecortave acetate versus photodynamic therapy for the treatment of age-related macular degeneration. One trial found posterior juxtrascleral depot of anecortave acetate may be effective in preventing severe vision loss. Overall the assessment noted weak evidence as to the benefits and harms of steroids with antiangiogenic properties for treating neovascular AMD by posterior juxtrascleral placement of drugs.

Use Outside of the US

No relevant information.

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Automated Evacuation of Meibomian Glands (CPT Code 0207T)

The meibomian glands are located on the eyelids and are responsible for the production of sebum. Sebum prevents the tear film from evaporating too quickly from the eye's surface. Meibomian gland dysfunction leads to decreased secretion and abnormal composition of the tear film lipid layer, which in turn can lead to blockage of the glands, dry eye, and infection. Conventional treatment includes eyelid washing, use of preservative-free tears, omega-3 dietary supplementation, topical and oral antibiotics, corticosteroids, warm compresses and gentle eyelid massage. The use of an automated heated compression device has been proposed as a treatment of meibomian gland dysfunction.

U.S. Food and Drug Administration

The LipiFlow Thermal Pulsation System (TearScience, Morrisville, NC) received FDA 510(k) clearance in July, 2011. This system is intended to be used by a physician in an in-office procedure. The FDA approval indicates "The LipiFlow Thermal Pulsation System is intended for the application of localized heat and pressure therapy in adult patients with chronic cystic conditions of the eyelids, including meibomian gland dysfunction (MGD) also known as evaporative dry eye or lipid deficiency dry eye."

Literature Review

Blackie, et al (2017) conducted a prospective, multicenter, open-label clinical trial that included 200 subjects (400 eyes) who were randomized to a single VTP treatment (treatment group) or twice-daily, 3-month, conventional warm compress and eyelid hygiene therapy (control group). Control group subjects received crossover VTP treatment at 3 months (crossover group). Effectiveness measures of meibomian gland secretion (MGS) and dry eye symptoms were evaluated at baseline and one, three, six, nine and 12 months. Subjects with inadequate symptom relief could receive additional meibomian gland dysfunction therapy after 3 (treatment group) and 6 months (crossover group). At three months, the treatment group had greater mean improvement in MGS ($P<0.0001$) and dry eye symptoms ($P=0.0068$), compared to controls. At 12 months, 86% of the treatment group had received only one VTP treatment, and sustained a mean improvement in MGS from 6.4 ± 3.7 (baseline) to 17.3 ± 9.1 ($P<0.0001$) and dry eye symptoms from 44.1 ± 20.4 to 21.6 ± 21.3 ($P<0.0001$); 89% of the crossover group had received only one VTP treatment with sustained mean improvement in MGS from 6.3 ± 3.6 to 18.4 ± 11.1 ($P<0.0001$) and dry eye symptoms from 49.1 ± 21.0 to 24.0 ± 23.2 ($P<0.0001$). Greater mean improvement in MGS was associated with less severe baseline MGS ($P=0.0017$) and shorter duration of time between diagnosis and treatment ($P=0.0378$). The authors concluded that a single VTP treatment can deliver a sustained mean improvement in meibomian gland function and mean reduction in dry eye symptoms, over 12 months.

To compare the effectiveness of a single LipiFlow treatment with combined lid warming and massage in patients with meibomian gland dysfunction (MGD), Finis et al. (2014) published results of a prospective, randomized, crossover, observer-masked clinical trial involving 40 subjects. Subjects were randomized to receive either a single LipiFlow treatment (LipiFlow group) or to perform standardized, twice-daily combined lid warming and massage (lid margin hygiene or control group) for three months. The primary outcome measure was improvement of subjective symptoms, as assessed by the Ocular Surface Disease Index (OSDI) scores. Secondary outcome measures included improvement of TFBUT, decreased tear osmolarity, increased LLT, and increased number of expressible meibomian glands. A total of 31 subjects completed the study. A total of 31 subjects completed the 3-month follow-up. At 1 and 3 months, patients in the LipiFlow treatment group had a significant reduction in Ocular Surface Disease Index (OSDI) scores compared with those in the lid-margin hygiene group ($p < .01$). Both treatments produced a significant improvement in expressible meibomian glands compared to the baseline parameters, but no significant difference was noted between the two groups. The other investigated objective parameters did not show a significant difference. The authors note while results of this small study suggest that a single LipiFlow treatment is as least as effective as a 3-month, twice-daily lid margin hygiene regimen for MGD, the study was observer-masked only, and a placebo effect may have confounded any improvements in subjective symptoms and other parameters in both groups. Study limitations include non-blinded design and small study size. Larger, blinded randomized clinical trials are required to determine impact on health outcomes.

Lane et al. (2012) conducted a study examining the safety and effectiveness of the LipiFlow System compared with the iHeat Warm Compress (WC) for adults with meibomian gland dysfunction. This was a prospective open-label, randomized, crossover multicenter clinical trial. One hundred thirty-nine subjects were randomized between LipiFlow ($n=69$) and WC control ($n=70$). Subjects in the LipiFlow group received a 12-minute LipiFlow treatment and were reexamined at one day, two weeks and four weeks. Control subjects received a five-minute iHeat treatment with instructions to perform the same treatment daily for two weeks. At two weeks, they crossed over and received the LipiFlow treatment. LipiFlow resulted in significant improvement in meibomian gland secretion at two and four weeks ($p < 0.05$). There was no change in meibomian gland secretion in the control group. Limitations to the study were the small population size. Results replicated in larger RCTs are required to demonstrate the ability to apply outcomes to the general population.

Mitra et al. (2005) reported results of a prospective, controlled, observer masked, single intervention trial in which 24 normal subjects were randomized into three groups: Group I: 10 minutes with the activated device, Group II: 10 minutes with the inactivated device, Group III: no intervention. The lipid layer thickness of each subject was measured prior and subsequent to the 10-minute period. A statistically significant increase in lipid layer thickness was seen in 87% of subjects in Group I ($p < 0.001$, left eye, $p < 0.003$, right eye.). Seventy-five percent of subjects experienced subjective improvement in ocular comfort. The authors note that meibomian therapy using this novel device results in increased lipid layer thickness. A limitation of this study was the small study population.

Korb et al. (2011) reported on a study attempting to determine the pressure required to express the first non-liquid material from nonfunctional lower lid meibomian glands, the pressure required to evacuate all of the expressible material from the glands, and the level of pain associated with these actions. Custom instrumentation was applied to the lower lid, exerting pressures from 1.0 to 150.0 pounds per square inch (psi). Pressure was monitored throughout the procedure as was pain level. The pressure required to obtain the first non-liquid material ranged between 5-40 pounds per square inch. Pain was the limiting factor for this treatment. Only 7% of the patients could tolerate the pressure necessary to administer complete expression of the non-liquid material.

Professional Societies/Organizations

American Academy of Ophthalmology (AAO) (2013): the AAO preferred practice patterns for dry eye syndrome do not include automated heated compression device has been proposed as a treatment of meibomian gland dysfunction.

Use Outside of the US

No relevant information.

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Insertion of Ocular Telescope Prosthesis Including Crystalline Lens (CPT Codes 0308T, HCPCS Code C1840)

The prosthetic intraocular telescope system is intended for the treatment of central vision loss (bilateral central scotomas) due to age-related macular degeneration (AMD). The device projects an image onto the part of the retina which is still healthy and can still see images. The device not intended to cure AMD, however it has the potential to improve quality of life and daily functioning for patients with end-stage AMD. The implantation inside the eye allows the patient to use natural eye movements to see, rather than head movements, which are required when using external magnification devices for AMD-related low vision.

U.S. Food and Drug Administration (FDA): The Implantable Miniature Telescope™ (VisionCare Ophthalmic Technologies, Saratoga, CA) received FDA premarket approval in July 2010. According to the FDA, this device is an implantable device which, when combined with the optics of the cornea, constitutes a telephoto system for improvement of visual acuity in patients with severe to profound vision impairment due to bilateral, end-stage, age-related macular degeneration (AMD). The implantable miniature telescope (IMT) is surgically implanted in the capsular bag and is held in position by haptic loops. The intraocular telescope is available in two models: Wide Angle (WA) 2.2X and Wide Angle (WA) 2.7X. Both models are indicated for monocular implant. The implanted eye provides central vision, while the fellow eye continues to be used for peripheral vision.

The initial FDA approval noted the device is intended to improve vision in patients 75 years of age or older with stable, severe to profound vision impairment caused by end-stage age-related macular degeneration. The device is indicated for (FDA, 2010):

- monocular implantation to improve vision in patients greater than or equal to 75 years of age with stable, severe to profound vision impairment (best corrected distance visual acuity 20/160 to 20/800) caused by bilateral central scotomas associated with endstage age-related macular degeneration.
- Patients must:
 - have retinal findings of geographic atrophy or disciform scar with foveal involvement, as determined by fluorescein angiography;
 - have evidence of visually significant cataract (> grade 2)

- agree to undergo presurgery training and assessment (typically 2 to 4 sessions) with low vision specialists (optometrist or occupational therapist) in the use of an external telescope sufficient for patient assessment and for the patient to make an informed decision;
- achieve at least a 5-letter improvement on the ETDRS chart with an external telescope;
- have adequate peripheral vision in the eye not scheduled for surgery; and 6) agree to participate in postoperative visual training with a low vision specialist.

In October 2014, the FDA expanded the age limit for Implantable Miniature Telescope (IMT) to 65 years of age or older. The supplement also included revisions to the professional and patient labeling with updated data based on the results out to eight years post IMT implantation; to revise the acceptance of risk and informed decision agreement; and to the professional and patient labeling to emphasize that the longer the IMT is in the eye, the greater the potential risk of developing vision-impairing corneal edema which may lead to the need for corneal transplant and possible telescope removal.

As part of the initial approval, there was a requirement for extended follow-up of the premarket cohort population. According to the FDA, this continued follow-up of individuals in the long-term follow-up cohort (5 years postoperatively) will be conducted to provide additional long-term (up to eight years) safety data. The FDA also requires a multicenter, prospective, open label, single group assignment cohort study for safety. The study is required to consecutively will enroll 770 presurgical subjects aged 75 years and older with severe to profound vision impairment caused by end-stage age-related macular degeneration and a cataract. The subjects enrolled and undergoing implantation of the IMT will be followed for a total of five years with approximately six follow-up visits during the first year followed by annual visits thereafter for the next four years (FDA, 2010).

According to the FDA Summary Of Safety And Effectiveness implantation of the device is contraindicated in patients (FDA, 2010):

- Stargardt's macular dystrophy
- central anterior chamber depth (ACD) <3.0 mm; measurement of the ACD should be taken from the posterior surface of the cornea (endothelium) to the anterior surface of the crystalline lens.
- presence of corneal guttata.
- minimum age and endothelial cell density requirements are not met
- with cognitive impairment that would interfere with the ability to understand and complete the Acceptance of Risk and Informed Decision Agreement or prevent proper visual training/rehabilitation with the device
- who have evidence of active choroidal neovascularization (CNV) on fluorescein angiography or treatment for CNV within the past six months
- with any ophthalmic pathology that compromises the patient's peripheral vision in the fellow eye
- with previous intraocular or cornea surgery of any kind in the operative eye, including any type of surgery for either refractive or therapeutic purposes
- who have prior or expected ophthalmic related surgery within 30 days preceding intraocular telescope implantation
- with a history of steroid-responsive rise in intraocular pressure (IOP), uncontrolled glaucoma, or preoperative IOP >22 mm Hg, while on maximum medication
- with known sensitivity to post-operative medications
- who have a history of eye rubbing or an ocular condition that predisposes them to eye rubbing
- in whom the planned operative eye has:
 - myopia > 6.0 D
 - hyperopia > 4.0 D
 - axial length < 21 mm
 - a narrow angle, i.e., < Schaffer grade 2
 - cornea stromal or endothelial dystrophies, including guttata
 - inflammatory ocular disease
 - zonular weakness/instability of crystalline lens, or pseudoexfoliation
 - diabetic retinopathy

- untreated retinal tears
- retinal vascular disease
- optic nerve disease
- a history of retinal detachment
- intraocular tumor
- retinitis pigmentosa.
- in eyes in which both haptics cannot be placed within the capsular bag during surgery, the intraocular telescope should be removed and replaced with a conventional intraocular lens (IOL); sulcus fixation of either one or both haptics increases the risk of severe endothelial cell loss and corneal transplant

Literature Review

Hudson et al. (2006) reported on a prospective, open-label, multicenter clinical trial (IMT-002 clinical trial) with fellow eye controls. The trial included 217 patients with AMD and moderate to profound bilateral central visual acuity loss (20/80-20/800) resulting from bilateral untreatable geographic atrophy, disciform scars. A visual prosthetic device (implantable telescope), designed to enlarge retinal images of the central visual field, was implanted monocularly in the capsular bag after lens extraction. Fellow eyes were not implanted to provide peripheral vision and served as controls. Study patients participated in six visual rehabilitation visits after surgery. At one year, 67% of implanted eyes achieved a 3-line or more improvement in best-corrected distance visual acuity (BCDVA) versus 13% of fellow eye controls ($P < 0.0001$). Fifty-three percent of implanted eyes achieved a 3-line or more improvement in both BCDVA and BCNVA versus 10% of fellow eyes ($P < 0.0001$). Mean BCDVA and best-corrected near visual acuity (BCNVA) improved 3.5 lines and 3.2 lines, respectively, in implanted eyes versus 0.8 lines and 1.8 lines, respectively, in fellow eyes ($P < 0.0001$). Eleven eyes did not receive the device because of an aborted procedure. Endothelial cell density was reduced by 20% at three months and 25% at one year. The decrease in Endothelial cell density (ECD) was correlated with postsurgical edema ($P < 0.0001$) with no evidence that endothelial cell loss is accelerated by ongoing endothelial trauma after implantation, the authors concluded that the device can improve visual acuity and quality of life in patients with moderate to profound visual impairment caused by bilateral, end-stage AMD.

Hudson et al. (2008) reported on two year results of the above study. The main outcome measures included BCVA change from baseline, endothelial cell density (ECD) and morphometry, and incidence of complications. At two years, data from 174 (92.6%) of 188 available patients were analyzed with findings that overall, 103 (59.5%) of 173 telescope-implanted eyes gained three lines or more (doubling of visual angle) of BCVA compared with 18 (10.3%) of 174 fellow control eyes ($P < .0001$). Mean BCVA improved 3.6 lines (standard deviation [SD], 1.9 lines) and 2.8 lines (SD, 2.3 lines) from baseline in eyes with the 3X and 2.2X device models, respectively. Mean ECD stabilized through two years, with 2.4% mean cell loss occurring from one to two years. There was no significant change in coefficient of variation or percentage of hexagonal endothelial cells from within six months to two years after surgery. The most common complication found to be inflammatory deposits. The authors concluded that long-term results of this telescope prosthesis indicate the substantial BCVA improvement at one year is maintained at two years with the key indicators of corneal health demonstrating ECD change that reflects remodeling of the endothelium associated with the implantation procedure and no that there is no evidence of any ongoing endothelial trauma.

Boyer et al. (2015) reported on the long-term results (60 months) of implantable miniature telescope (IMT) in patients with bilateral, end-stage, age-related macular degeneration (AMD) (studies above Hudson, et al., 2006; Hudson et al., 2008). A subgroup analysis was performed with stratification for age (patient age 65 to <75 years [group 1; n=70] and patient age ≥ 75 years [group 2; n=127]), with a comparative evaluation of change in best-corrected distance visual acuity (BCDVA), quality of life, ocular complications from surgery, adverse events, and endothelial cell density (ECD). The mean BCDVA improvement from baseline to 60 months was 2.41 ± 2.69 lines in all patients (n=76), with 2.64 ± 2.55 lines in group 1 and 2.09 ± 2.88 lines in group 2. The quality of life scores were significantly higher in group 1. The most common significant surgery-related ocular complications in group 1 were iritis >30 days after surgery (7/70; 10%) and persistent corneal edema (3/70; 4.3%); and in group 2 were a decrease in BCDVA in the implanted eye or IMT removal (10/127 each; 7.9%), corneal edema >30 days after surgery (9/127; 7.1%), and persistent corneal edema (6/127; 4.7%). The significant adverse events included four corneal transplants, comprising two (2.9%) in group 1 and two (1.6%) in group 2. At 60 months, one patient in group 1 (3.2%) and three patients in group 2 (9.4%) had lost ≥ 2 lines of vision. The IMT was removed in one (1.4%) and ten (7.9%) patients in group 1 and group 2, respectively. Mean ECD loss was 20% at 3 months.

Chronic loss was 3% per year. ECD loss was less in group 1 than in group 2 (35% versus 40%, respectively) at 60 months. These long-term results indicate substantial retention of improvement in BDCVA. The chronic ECD loss appears consistent with that reported for conventional intraocular lenses. The results indicate that younger patients retained more vision than their older counterparts with fewer adverse events.

Use Outside of the US

National Institute for Health and Care Excellence (NICE) published guidelines for miniature lens system implantation for advanced age-related macular degeneration. The guidelines note (NICE, 2016) that, "Evidence on the efficacy of miniature lens system implantation for advanced age-related macular degeneration (AMD) shows that the procedure can improve both vision and quality of life in the short term. Data on short-term safety are available for limited numbers of patients. There is currently insufficient long-term evidence on both efficacy and safety. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research."

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Quantitative Pupillometry (CPT Code 0341T)

Pupil reactivity and sensitivity may indicate neurological issues or worsening of neurological status. Current practice is to use a penlight to observe the pupillary light reflex which is a subjective measurement. Several quantitative pupillometer devices are available, although their use is primarily restricted to the research setting (Courét, et al., 2016). The stimulation and subsequent measurement of pupil reactivity by a hand held infrared camera and use of a digital device and data processor to calculate measurements has been proposed for a number of indications including the evaluation of autonomic function, response to pain, drug metabolism, sleep disorders, and various psychological indications and has been used in the research setting. A pupillometer is made of three components: the light source to stimulate the pupil, an image capturing device capable of taking measurements of the pupil in real-time, and a data processor that performs the calculations using the measurements. The device is held in the patient's visual field, the data is interpreted, and a report is generated.

Literature Review

High level, randomized and controlled data are lacking regarding the effectiveness of this device in the published, peer viewed scientific literature.

Couret et al. (2016) reported on study that compared automated quantitative pupillometry with the standard clinical pupillary examination currently used for brain-injured patients. Repetitive measurements were made in 200 healthy volunteers providing a total of 400 paired (alternative right eye, left eye) measurements under a wide variety of ambient light condition with the NeuroLight Algiscan pupillometer and then a prospective, observational, double-blinded study was conducted in two neurocritical care units. In 200 healthy volunteers, intra-class correlation coefficient for maximum resting pupil size was 0.95 (IC: 0.93-0.97) and for minimum pupil size after light stimulation 0.87 (0.83–0.89). It was found 3-pupil asymmetry (≥ 1 mm) in these volunteers (1.5 % of the population) with a clear pupil asymmetry during clinical inspection. The mean pupil light reactivity was 40 ± 7 %. In 59 patients, 406 pupillary measurements were prospectively performed. Concordance between measurements for pupil size collected using the pupillometer, versus subjective assessment, was poor (Spearman's rho = 0.75, IC: 0.70-0.79; $P < 0.001$). A global rate of discordance of 18 % (72/406) was found between the two techniques when assessing the pupillary light reflex. For measurements with small pupils (diameters < 2 mm) the error rate was 39 % (24/61). The results demonstrated that pupillary evaluations obtained subjectively at the patient's bedside were inaccurate compared with those obtained with an automatic quantitative pupillometer device. The authors concluded that the standard practice in pupillary monitoring yields inaccurate data, that automated quantitative pupillometry is a appears to be a more reliable method with which to collect pupillary measurements at the bedside; however, the impact of a pupillometer use on patients' outcome has to be demonstrated in further prospective studies.

In a cross-sectional cohort study Kantor et al. (2014) assessed the association between postoperative pain (NRS) and pupillary diameter or pupillary light reflex amplitude (PLRA) in 145 Post Anesthesia Care Unit (PACU) patients after routine anesthetic care. Sedation, hemodynamic, pupillary and pain assessments were performed in each patient after their arrival in the PACU or before morphine titration. In patients receiving morphine titration, a second assessment was performed after titration. Sedation was assessed using the modified Observer's Assessment of Alertness/Sedation (OAAS) scale. Hemodynamic assessment consisted of non-invasive systolic and diastolic blood pressure and heart rate. Pupillary assessment was performed with an infrared portable dynamic videopupillometer. Mean numerical rating score (NRS) for pain as assessed by study participants was 4.7, and was more than four in 79 patients (55%). No statistically significant association was observed between NRS and pupillary diameter ($p=0.54$). Twenty-seven patients (19%) received morphine titration with significant decreases in NRS, pupillary diameter and PLRA afterwards. No association was observed between NRS changes and pupillary diameter or PLRA changes. The authors concluded acute postoperative pain is not associated with pupillary diameter or PLRA. Further high quality randomized clinical trial data is required to demonstrate the impact of pupillometry as a means to assess pain in the PACU.

Bremner et al. (2006) reported results of a prospective study of involving the use of light reflex pupillography in 150 consecutive patients with symptomatic generalized autonomic failure. Inclusion criteria was heterogeneous with a variety of indications represented including amyloidosis, multiple system atrophy, pure autonomic failure, diabetes mellitus, hereditary neuropathies, and paraneoplastic syndromes. Infra-red video pupillography was used to measure resting pupil diameters in light and dark, the light reflex response, the miosis associated with an accommodative effort, and responses to topical administration of various pharmacological agents. No significant correlation between the type of pupil abnormality and the predominant type of systemic autonomic deficit was seen in most conditions. The authors note "Although there does appear to be some weak correspondence between our pupillographic findings and the results of autonomic function tests, a x2 test suggests that this association could have arisen by chance ($p=0.072$)."

Professional Societies/Organizations

American Academy of Ophthalmology (AAO) (2013): The Guidelines for recommendations for keratorefractive laser surgery notes that measurement of pupil size is not required in the preoperative examination.

Use Outside of the US

No relevant information

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Visual Field Assessment with Concurrent Real Time Data Analysis (CPT Codes 0378T, 0379T)

Visual field assessment is reported for up to 30 days. The patient transmits daily test-data to monitoring center (IDTF) for input into secured database. The technician with physician analyzes the data and prepares report and the results are then interpreted by a physician.

Literature Review

There is insufficient evidence in the published, peer-reviewed scientific literature to establish improved health outcomes with this testing. At this time the role of this service has not been established.

Professional Societies/Organizations

Professional society guidelines are lacking regarding visual field assessment with concurrent real time data analysis.

Use Outside of the US

No relevant information

References

Computer-Aided Animation and Analysis of Time Series Retinal Images for the Monitoring of Disease Progression (CPT Code 0380T)

MatchedFlicker® (EyelC Inc., Wayne, PA) is a device that is purported to enable fast and accurate comparison of digital fundus images to aid clinicians in diagnosis. According to the vendor's website, MatchedFlicker automatically combines time-series images selected from a patient record to create an animation wherein images are aligned, superimposed and alternated back and forth.

There is insufficient evidence in the published, peer-reviewed scientific literature to establish improved health outcomes using this technology. At this time the role of computer-aided animation and analysis of time series retinal images to monitor disease progression has not been established.

Literature Review

There is insufficient evidence in the published, peer-reviewed scientific literature to establish improved health outcomes with this testing. At this time the role of this service has not been established.

Professional Societies/Organizations

Professional society guidelines are lacking regarding computer-aided animation and analysis of time series retinal images for the monitoring of disease progression.

Use Outside of the US

No relevant information

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Retinal prosthesis system (Device evaluation, interrogation, and initial programming of intra-ocular retinal electrode array) (CPT codes 0100T, 0472T, 0473T, C1841, C1842)

Retinitis pigmentosa (RP) comprises a complex group of inherited dystrophies characterized by progressive degeneration and dysfunction of the retina, primarily affecting photoreceptor and pigment epithelial function. The clinical manifestations of RP include night blindness, loss of peripheral vision from progressive loss of photoreceptors, and variably loss of central vision due to cataracts and macular edema (Garg [UpToDate], 2017). The Argus II Retinal Prosthesis System (Argus II) (Second Sight Medical Products, Inc. Sylmar, CA) is intended to provide electrical stimulation of the retina to elicit visual perception in blind individuals with severe to profound retinitis pigmentosa. The implant is an epiretinal prosthesis that is surgically implanted in and on the eye that includes an antenna, an electronics case, and an electrode array. The external equipment includes glasses, a video processing unit (VPU) and a cable.

U.S. Food and Drug Administration (FDA): The Argus II Retinal Prosthesis System received a Humanitarian Device Exemption (HDE) from the FDA in February 2013. This device is indicated for use in patients with severe to profound retinitis pigmentosa who meet the following criteria:

- Adults, age 25 years or older.
- Bare light or no light perception in both eyes. (If the patient has no residual light perception, then evidence of intact inner layer retina function must be confirmed.)
- Previous history of useful form vision.
- Aphakic or pseudophakic. (If the patient is phakic prior to implant, the natural lens will be removed during the implant procedure.)
- Patients who are willing and able to receive the recommended post-implant clinical follow-up, device fitting, and visual rehabilitation.

Literature Review

Agency for Healthcare Research and Quality (AHRQ) published a technology assessment for retinal prostheses systems (RPS) in the Medicare population (Fontanarosa, et al., 2016). The review included 30 publications of 11 RPS studies. The report notes that, "Although some patients clearly experienced improved visual acuity, visual field, and visual function, the percentages varied greatly among studies of Moderate to High risk of bias. Thus, evidence is insufficient to estimate the proportion of patients who will benefit from an RPS." The report concluded that some patients clearly benefit from implantation with an RPS, but determining who those patients are is still a challenge. Future studies of retinal prostheses devices should make an effort to report valid and reliable measures of important outcomes, especially day-to-day function and quality of life (QoL).

Dagnelie et al. (2017) conducted a study with the objective to test 28 Argus II subjects, all profoundly blind on three real-world functional vision tasks. Subjects were tested on the three real-world functional vision tasks: Sock Sorting, Sidewalk Tracking and Walking Direction Discrimination task. The mean percentage correct OFF versus ON for the Sock Sorting task was found to be significantly different for both testing conditions (t-test, $P < 0.01$). On the Sidewalk Tracking task, subjects performed significantly better with the system ON than they did with the system OFF (t-test, $P < 0.05$). Eighteen (18) of 27 subjects (67%) performed above chance with the system ON, and 6 (22%) did so with system OFF on the Walking Direction Discrimination task. The authors concluded that Argus II subjects performed better on all three tasks with their systems ON than they did with their systems OFF. The study is limited by the small number of subjects and needs to be confirmed in a larger study.

Da Cruz conducted a prospective, multicenter, single-arm, clinical trial of 30 subjects in 10 centers in US and Europe to study the long-term safety and efficacy of the Argus II System in patients with bare or no light perception due to end-stage RP. Within-patient controls included the non-implanted fellow eye and patients' native residual vision compared to their vision when using the System. The primary outcome measures were safety (the number, seriousness, and relatedness of adverse events) and visual function, as measured by three computer-based, objective tests. Secondary measures included functional vision performance on objectively-

scored real-world tasks. Twenty-four out of 30 patients remained implanted with functioning Argus II Systems at 5 years post-implant. Only one additional serious adverse event was experienced since the three-year time point. Patients performed better with the System ON than OFF on all visual function tests and functional vision tasks. The authors concluded that the five-year results of the Argus II trial support the long-term safety profile and benefit of the Argus II System for patients blind from RP.

Professional Societies/Organizations

Professional society guidelines are lacking regarding intra-ocular retinal electrode array for treatment of retinitis pigmentosa.

Use Outside of the US

Health Quality Ontario: this organization published a health technology assessment for retinal prosthesis system for advanced retinitis pigmentosa (2017). The recommendation of the assessment notes, "The Ontario Health Technology Advisory Committee recommends publicly funding the Argus II retinal prosthesis system for advanced retinitis pigmentosa." The committee determined that the Argus II system has demonstrated clinical effectiveness in restoring partial functional vision for patients with advanced retinitis pigmentosa. The Ontario Health Technology Advisory Committee took into account value for money, as well as the lived experience of people with retinitis pigmentosa and noted that the Argus II system offers the possibility of quality-of-life improvements in a population for whom there is no other treatment option.

National Institute for Health and Care Excellence (NICE): NICE published interventional procedure guidance for insertion of epiretinal prosthesis and insertion of a subretinal prosthesis system for retinitis pigmentosa (NICE, 2015). The guidance includes these recommendations:

Subretinal prosthesis system:

- Current evidence on the safety and efficacy of insertion of a subretinal prosthesis system for retinitis pigmentosa is limited in quality and quantity. Therefore, this procedure should only be used in the context of research.
- NICE encourages further research on this procedure. Outcomes should include the impact on quality of life and activities of day-to-day living, and durability of implants.

Epiretinal prosthesis:

- Current evidence on the safety and efficacy of insertion of epiretinal prosthesis for retinitis pigmentosa is limited in quality and quantity. Therefore, this procedure should only be used in the context of research.
- NICE encourages further research on this technology. Outcomes should include the impact on quality of life and activities of day-to-day living, and durability of implants.

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Coding/Billing Information Ophthalmology

Note: 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Insertion of Ocular Telescope Prosthesis Including Crystalline Lens

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

| CPT® Codes | Description |
|-------------------|---------------------------------------------------------------------------------------------------------------|
| <u>0308T</u> | Insertion of ocular telescope prosthesis including removal of crystalline lens or intraocular lens prosthesis |

| HCPCS Codes | Description |
|--------------------|--------------------------------|
| C1840 | Lens, intraocular (telescopic) |

Ophthalmology Services Considered Experimental/Investigational/Unproven:

| CPT® Codes | Description | Comment |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <u>67299</u> | Unlisted procedure, posterior segment | Considered Experimental/Investigational/Unproven when used to report suprachoroidal delivery of pharmacologic agent |
| <u>68399</u> | Unlisted procedure, conjunctiva | Considered Experimental/Investigational/Unproven when used to report conjunctival incision with posterior extracapsular placement of a pharmacologic agent |
| <u>0100T</u> | Placement of a subconjunctival retinal prosthesis receiver and pulse generator, and implantation of intra-ocular retinal electrode array, with vitrectomy | |
| <u>0207T</u> | Evacuation of meibomian glands, automated, using heat and | |

| | | |
|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| | intermittent pressure, unilateral | |
| <u>0341T</u> | Quantitative pupillometry with interpretation and report, unilateral or bilateral | |
| <u>0378T</u> | Visual field assessment, with concurrent real time data analysis and accessible data storage with patient initiated data transmitted to a remote surveillance center for up to 30 days; review and interpretation with report by a physician or other qualified health care professional | |
| <u>0379T</u> | Visual field assessment, with concurrent real time data analysis and accessible data storage with patient initiated data transmitted to a remote surveillance center for up to 30 days; technical support and patient instructions, surveillance, analysis, and transmission of daily and emergent data reports as prescribed by a physician or other qualified health care professional | |
| <u>0380T</u> | Computer-aided animation and analysis of time series retinal images for the monitoring of disease progression, unilateral or bilateral, with interpretation and report | |
| <u>0465T</u> | Suprachoroidal injection of a pharmacologic agent (does not include supply of medication) | |
| <u>0472T</u> | Device evaluation, interrogation, and initial programming of intraocular retinal electrode array (eg, retinal prosthesis), in person, with iterative adjustment of the implantable device to test functionality, select optimal permanent programmed values with analysis, including visual training, with review and report by a qualified health care professional | |
| <u>0473T</u> | Device evaluation and interrogation of intraocular retinal electrode array (eg, retinal prosthesis), in person, including reprogramming and visual training, when performed, with review and report by a qualified health care professional | |

| HCPSC Codes | Description |
|-------------|------------------------------------------------------------------------------------|
| C1841 | Retinal prosthesis, includes all internal and external components |
| C1842 | Retinal prosthesis, includes all internal and external components; add-on to C1841 |

*Current Procedural Terminology (CPT®) ©2017 American Medical Association: Chicago, IL.

Oncology

Tumor Treatment Fields Therapy (e.g., Optune™) (HCPSC Codes A4555, E0766)

Electric tumor treatment fields (TTF) therapy, also known as alternating electric field therapy, has been proposed for the treatment of recurrent glioblastoma multiforme (GBM). Inferred mechanism of action is disruption of the rapid cell division exhibited by cancer cells by alternating electrical currents applied to the brain through electrically insulated surface transducer arrays which are placed on the patient's shaved scalp. The fields alter the tumor cell polarity at an intermediate frequency. The frequency used for a particular treatment is specific to the cell type being treated (NovoCure, 2014).

At this time, Optune™ (formerly the NovoTTF-100A System) (Novocure, Portsmouth, NH) is the only TTF device that has received FDA approval electric tumor fields therapy. This system is a wearable, non-invasive, portable battery or power-supply operated device designed for continuous use throughout the day or night. It produces continuous TTF treatment at 100-200kHz. TTF are applied to two pairs of insulated electrode arrays in an alternating fashion. The electrodes are placed on the scalp over a layer of adhesive hydrogel which is held in place by adhesive strips. The scalp must be re-shaved to maintain optimal contact between the electrode and

the skin. Gel under the electrodes requires replacement every three-four days. The treatment period is for a minimum of four weeks.

U.S. Food and Drug Administration (FDA)

The NovoTTF-100A System (Portsmouth, NH) was granted premarket approval (PMA) by the FDA in April, 2011. This device is indicated for treatment of adult patients who are 22 years of age or older who have histologically-confirmed glioblastoma multiforme (GBM), following histologically-or radiologically confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted. The pre-market approval requires a post market nonrandomized, unblinded, concurrent control study to be undertaken using the NovoTTF-100A system in patients with recurrent GBM (FDA, 2011).

In October 2015, the FDA approved an expanded indication for the Optune device to treat patients with newly-diagnosed glioblastoma multiforme (GBM), an aggressive form of brain cancer. It is given along with the chemotherapy drug temozolomide (TMZ) following standard treatments that include surgery, and radiation therapy and chemotherapy used together.

Literature Review

Stupp et al. (2015) reported on an interim analysis of a multicenter, open-label, randomized phase 3 trial designed to test the efficacy and safety of TTFields in combination with temozolomide for treatment of glioblastoma after initial treatment with chemoradiation. The study included 210 patients randomized to TTFields plus temozolomide and 105 patients randomized to temozolomide alone, and conducted at a median follow-up of 38 months. Results included that median progression-free survival in the intent-to-treat population was 7.1 months (95%CI, 5.9-8.2 months) in the TTFields plus temozolomide group and 4.0 months (95%CI, 3.3-5.2 months) in the temozolomide alone group (hazard ratio [HR], 0.62 [98.7%CI, 0.43-0.89]; $P=.001$). Median overall survival in the per-protocol population was 20.5 months (95%CI, 16.7-25.0 months) in the TTFields plus temozolomide group ($n=196$) and 15.6 months (95%CI, 13.3-19.1 months) in the temozolomide alone group ($n=84$) (HR, 0.64 [99.4%CI, 0.42-0.98]; $P=.004$). The authors concluded that in this analysis of patient with glioblastoma who had completed standard chemoradiation therapy, the addition of TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival.

Stupp et al. (2017) reported on the final analysis randomized, trial noted above (Stupp, et al., 2015) of all 695 patients with median follow-up of 40 months and minimum follow-up of 24 months. Patients were randomized 2:1 to TTFields plus maintenance temozolomide chemotherapy ($n = 466$) or temozolomide alone ($n = 229$). The TTFields, consisting of low-intensity, 200 kHz frequency, alternating electric fields, was delivered (≥ 18 hours/d) via 4 transducer arrays on the shaved scalp and connected to a portable device. Temozolomide was administered to both groups for 5 days per 28-day cycle (6-12 cycles). Progression-free survival (tested at $\alpha = .046$). The secondary end point was overall survival (tested hierarchically at $\alpha = .048$). Analyses were performed for the intent-to-treat population. Of the 695 patients 637 (92%) completed the trial. Median progression-free survival from randomization was 6.7 months in the TTFields-temozolomide group and 4.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.52-0.76; $P < .001$). Median overall survival was 20.9 months in the TTFields-temozolomide group vs 16.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76; $P < .001$). Systemic adverse event frequency was 48% in the TTFields-temozolomide group and 44% in the temozolomide-alone group. Mild to moderate skin toxicity underneath the transducer arrays occurred in 52% of patients who received TTFields-temozolomide compared to none in patients who received temozolomide alone.

Hayes published a directory report regarding Tumor Treating Fields (TTF) (Hayes, March 2016; 2018). The review concluded that although clinical trials have shown that Novocure is at least comparable with chemotherapy, the body of literature is small and individual studies are subject to serious limitations, including lack of a control or comparator group, high loss to follow-up, and lack of statistical comparisons. Additional evidence including randomized, controlled trials and cohort studies of sufficient size and design are needed to further investigate the safety and efficacy of Novocure in patients with recurrent and newly diagnosed glioblastoma and other cancers.

Data regarding the safety and effectiveness for TTF are limited in the published, peer-reviewed scientific literature and consist of several prospective studies and a randomized clinical trial (RCT) involving a total of 273 patients (Stupp, 2012; Kirson, 2009; Salzberg, 2008; Kirson, 2007). In the prospective phase III RCT, Stupp et al. (2012) reported results of 237 individuals with recurrent GBM. Participants were randomized to TTF (n=120) versus physician's choice of chemotherapy (n=117). The study failed to reach its primary end-point of improved survival compared to active chemotherapy. Neither overall survival nor progression-free survival were significantly improved at six months in the group randomized to TTF versus chemotherapy (p=0.23 and 0.13, respectively). The authors noted that responses were more frequent in the group treated with TTF but this was not significant (p=0.19). Quality of life measurement favored TTF over chemotherapy for emotional and cognitive functioning; no significant difference was noted for global health and social functioning. Physical functioning favored the chemotherapy arm. TTF-related adverse events were mild (14%) to moderate (2%), usually involving skin rash beneath the transducer arrays. Severe adverse events occurred in 6% and 16% (p = 0.022) of patients treated with TTF and chemotherapy, respectively. Results do not demonstrate improved OS or PFS with TTF compared to active chemotherapy.

NovoTAL™ (CPT code 64999)

NovoTAL (Novocure, Portsmouth, NH) is software that may be used for treatment planning before the Optune treatment. According to vendor's website, NovoTAL is optional software that a physician can purchase and create individualized treatment maps for patients starting Optune. It is performed in-office. The physicians are required to complete training and certification in order to use the NovoTAL System. The Optune device is available preset from Novocure. The device is preset to deliver TTF fields at a frequency of 200 kHz and is operated by the patient independently. It is monitored periodically by device specialists, who are available 24/7 to provide technical support to the patient, their family and physician (Trusheim, et al., 2017). The published literature does not indicate that the use of the software for treatment planning with Novotal is superior to using Optune with preset settings or that it improves clinical outcomes.

Literature Review—NovoTAL

Wenger et al. (2016) reported on a study with a human head model generated from MRI images of a healthy subject to investigate tumors of different size, shape, and location and the effect of varying transducer layouts on Tumor Treating Fields (TTF) distribution in an anisotropic model. Four different virtual tumors were placed at separate locations. The transducer arrays were modeled to mimic the TTF-delivering commercial device. For each tumor location, varying array layouts were tested. The finite element method was used to calculate the electric field distribution, taking into account tissue heterogeneity and anisotropy. In all tumors, the average electric field induced by either of the two perpendicular array layouts exceeded the 1-V/cm therapeutic threshold value for TTF effectiveness. Field strength within a tumor did not correlate with its size and shape but was higher in more superficial tumors. Additionally, it always increased when the array was adapted to the tumor's location. Compared with a default layout, the largest increase in field strength was 184%, and the highest average field strength induced in a tumor was 2.21 V/cm. The authors concluded that the result adapting transducer array layouts to specific tumor locations was highly beneficial, because it led to substantial increases in the induced field strength within the tumor and better TTF coverage in the affected areas.

Connelly et al. (2016) reported on a case series of eight patients where treating physician has utilized non-contrast enhancement and advanced imaging to inform tumor treatment fields (TTF) treatment planning based on a clinical evaluation of where a patient is believed to have active tumor. All patients presented with gliomas (grades 2–4). Each patient had previously received standard therapy including surgery, radiation therapy and/or chemotherapy prior to initiation of TTF and the majority had progressed on prior therapy. A standard pre- and postcontrast MRI scan was acquired and used for TTF treatment planning. The authors concluded that the case series details important approaches for integrating clinical considerations, nonmeasurable disease and advanced imaging into the treatment planning workflow for TTF. The author noted that as TTF become integrated into standard care pathways for glioblastoma, the case series demonstrates that treatment planning beyond the extent of contrast enhancement is clinically feasible and should be prospectively compared to standard treatment planning in a clinical trial setting, in order to determine the impact on patient outcomes.

Chaudry et al. (2015) reported on a study that evaluated performance of 14 physicians in conducting transducer array layout mapping using the NovoTAL System compared with mapping performed by the Novocure in-house clinical team. The physicians evaluated five blinded cases of recurrent glioblastoma and performed head size

and tumor location measurements using a standard Digital Imaging and Communications in Medicine reader. Concordance with Novocure measurement and intra- and inter-rater reliability were assessed using relevant correlation coefficients. The study criterion for success was a concordance correlation coefficient (CCC) >0.80. CCC for each physician versus Novocure on 20 MRI measurements was 0.96 (standard deviation, SD \pm 0.03, range 0.90–1.00). Intra- and inter-rater reliability correlation coefficients were similarly high: 0.83 (SD \pm 0.15, range 0.54–1.00) and 0.80 (SD \pm 0.18, range 0.48–1.00), respectively. This user study has a low number of participants and while it appears that there is a high agreement between the two groups, it does not indicate that NovoTAL provides improved health outcomes compared to mapping provided by Novocure.

Professional Societies/Organizations

National Comprehensive Cancer Network™ (NCCN™): NCCN guideline for cancer of the central nervous system includes in the recommendation for treatment of recurrent disease, the option to consider alternating electric field therapy for recurrent disease for anaplastic oligodendroglioma, anaplastic oligoastrocytoma, anaplastic astrocytoma, and glioblastoma. Category 2B*

The 2018 update of the NCCN guidelines includes in the recommendation for treatment of glioblastoma (with supratentorial disease), adjuvant treatment, the option of using adjuvant temozolomide and alternating electric field therapy. Category 1*

*NCCN Categories of Evidence and Consensus:

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate (NCCNa, 2018).

Use Outside of the US

A second generation Optune device has received placement of the CE Mark for use in the European Union.

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Coding/Billing Information Oncology

Note: 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Tumor Treatment Fields (TTF) Therapy (i.e., Optune™)

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

| HCPCS Codes | Description |
|--------------------|-------------------------------------------------------------------------------------------------------------|
| <u>A4555</u> | Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only |
| <u>E0766</u> | Electrical stimulation device used for cancer treatment, includes all accessories, any type |

Considered Experimental/Investigational/Unproven when used to report treatment planning software (i.e., NovoTAL) for use with tumor treatment fields:

| CPT® Codes | Description | Comment |
|-------------------|------------------------------------|------------------------------------------|
| <u>64999</u> | Unlisted procedure, nervous system | Considered Experimental/Investigational/ |

| | | |
|--|--|--------------------------------------------------------------------------------------------------------------|
| | | Unproven when used to report treatment planning software (i.e., NovoTAL) for use with tumor treatment fields |
|--|--|--------------------------------------------------------------------------------------------------------------|

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Otolaryngology

Automated Audiometry Devices (CPT Codes 0208T, 0209T, 0210T, 0211T, 0212T)

Audiometers measure and characterize hearing loss by determining an individual's hearing threshold. Conventional tests utilized for assessment include the behavioral pure-tone audiogram (hearing sensitivity of single-frequency signals) and speech recognition (hearing sensitivity for spoken material). These tests require interaction between the trained technician or audiologist and the patient. Conventional audiometry tests are performed manually and interpretation of the raw data is performed by the audiologist.

The use of automated audiometry devices has been proposed as an alternative to manually operated devices. Automated units use conventional technology; however, the equipment is fully automated. Results are displayed as pass or fail/refer and do not require further interpretation by a technician or audiologist. A failure score may result in further referral to a health care professional.

U.S. Food and Drug Administration (FDA)

Several automated audiometric devices have received FDA 510 (k) approval. These include, but are not limited to: the AuDX Otoacoustic Emissions Measurement System with AuDX I/O Function (Natus Medical Incorporated, Mundelein, IL) received FDA 510(k) approval as an equivalent device in December 2011. The device is indicated for use when it is necessary for a trained health care professional to measure or determine cochlear function. The device can be used for patients of all ages, from newborn infants through adults to include geriatric patients. The otoacoustic emissions test is especially indicated for use in testing individuals for whom behavioral results are deemed unreliable, such as infants, young children, and cognitively impaired adults. The Otogram™ Hearing Diagnostic System (Ototronix Diagnostics, Houston, TX, formerly marketed by Tympany, Inc., Salt Lake City, UT) received FDA 510(k) approval as an equivalent device in March 2007. The device is indicated for use by trained healthcare professionals on both adults and pediatric subjects for measurement of audiometric parameters to identify and supply to help diagnose hearing loss and ear disorders.

Literature Review

Although there are a number of cohort and case series reported in the published peer-reviewed scientific literature, randomized controlled trial, meta-analysis and systematic review data are lacking. In a nonrandomized comparison study by Lancaster et al. (2008) involving screening results of 32 children using on-site and telehealth screening methods the authors report identical otoscopic and immittance results. Pure-tone results were different between on-site and telehealth screening methods for five of 32 students. Using the on-site pure-tone screening protocol as the 'gold standard' the authors report that the tele-health pure-tone screening protocol yielded four false positive responses and one false negative response. This study was limited by uncontrolled study design and small study numbers.

Professional Societies/Organizations

American Academy of Pediatrics (AAP): The AAP (Harlor, et al., 2009) published recommendations for hearing assessment in infants and children. These recommendations include discussion of automated auditory brainstem response (ABR) test as an objective physiologic means of hearing screening. The guideline does not mention the automation of other tests.

Use Outside of the US

No relevant information.

References